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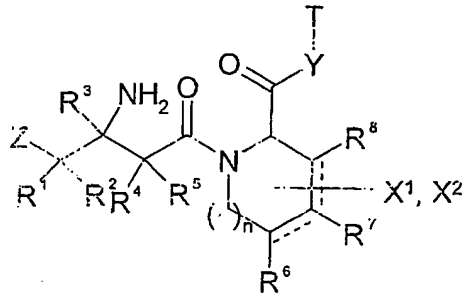
(54) Title: DPP-IV INHIBITORS



(I)

(57) Abstract: The invention relates to compounds of formula (I)wherein a dotted line indicates an optionally present double bond and wherein Z, R^1 - R^8, n, X^1, X^2, Y and T have the meaning as cited in the description and the claims. Said compounds are useful as DPP-IV inhibitors. The invention also relates to the preparation of such compounds as well as the production and use thereof as medicament.

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DPP-IV inhibitors

The present invention relates to a novel class of dipeptidyl peptidase inhibitors, including pharmaceutically acceptable salts and prodrugs thereof, which are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, often referred to as non-insulin dependent diabetes mellitus (NIDDM), and of conditions that are often associated with this disease, such as obesity and lipid disorders. The invention also relates to a process for the preparation of such inhibitors.

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at an increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In Type 1, or insulin-dependent, diabetes mellitus (IDDM), patients produce little or no insulin, which is the hormone regulating glucose utilization. In Type 2, or noninsulin dependent, diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or elevated compared to nondiabetic subjects. These patients develop a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, namely the muscle, liver and adipose tissues. Further, the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle, and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g., tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β-cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance, due to the even higher plasma insulin levels, can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhoea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (*i.e.*, 5-benzylthiazolidine-2,4-diones) are a recently described class of compounds with potential for ameliorating many symptoms of Type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of Type 2 diabetes, resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type 2 diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones

(*i.e.*, they are not thiazolidinediones). Serious side effects (*e.g.*, liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (*e.g.*, acarbose) and protein tyrosine phosphatase-IB (PTP-1B) inhibitors.

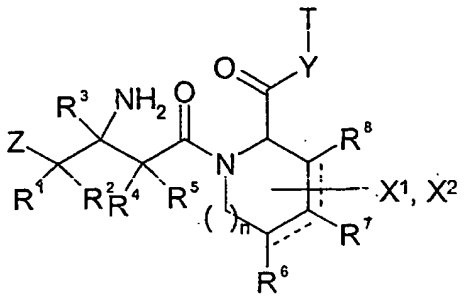
Compounds that are inhibitors of the dipeptidyl peptidase-IV (DPP-IV) enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly Type 2 diabetes. See for example WO-A-97/40832, WO-A-98/19998, WO-A-03/180 and WO-A-03/181. The usefulness of DPP-IV inhibitors in the treatment of Type 2 diabetes is based on the fact that DPP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DPP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DPP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DPP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DPP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

DPP-IV inhibitors may also have other therapeutic utilities, as discussed elsewhere in this application. DPP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPP-IV inhibitors can be found for the treatment of diabetes and potentially other disease and conditions.

Thus, the object of the present invention is to provide a new class of DPP-IV inhibitors which may be effective in the treatment of Type 2 diabetes and other DPP-IV modulated diseases.

Accordingly, the present invention provides novel compounds of formula (I) as defined in the claims.

Preferably, the present invention provides novel compounds of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein a dotted line indicates an optionally present double bond and wherein

Z is selected from the group consisting of
phenyl;
naphthyl;
C_{3-7} cycloalkyl;
heterocycle; and
heterobicycle;
wherein Z is optionally substituted with one, or independently from each other, more of
halogen;
N;
OH;
=O, where the ring is at least partially saturated;
C_{1-6} alkyl, optionally substituted with one or more F; and
O-C_{1-6} alkyl, optionally substituted with one or more F;

R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of
H;
F;
OH;
C_{1-6} alkyl, optionally substituted with one or more F; and

O-C_{1-6} alkyl, optionally substituted with one or more F;
and/or R^1 and R^2 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^2 and R^3 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^3 and R^4 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^4 and R^5 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

R^3 is H or C_{1-6} alkyl;

n is 0, 1 or 2;

X^1 is selected from the group consisting of
H;
F;
OH; and
C_{1-6} alkyl, optionally substituted with one or more F;

X^2 is selected from the group consisting of
H;
F; and
C_{1-6} alkyl, optionally substituted with one or more F;

R^6 and R^7 form together a ring A, provided that R^8 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more F;
or
R^8 and R^7 form together a ring A, provided that R^6 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more F;

A is selected from the group consisting of
phenyl;

wherein phenyl is optionally substituted with one or independently from each other, more of

halogen;

CN;

COOH;

OH;

$C(O)NH_2$;

$S(O)_2NH_2$;

C_{1-6} alkyl;

O-C_{1-6} alkyl;

COO-C_{1-6} alkyl;

OC(O)- C_{1-6} alkyl;

$C(O)N(R^9)$- C_{1-6} alkyl;

$S(O)_2N(R^{10})$-C_{1-6} alkyl;

$S(O)_2$-C_{1-6} alkyl; or

$N(R^{11})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one or more F;

heterocycle; and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl and heterocycle are optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;

NH_2

COOH;

$C(O)NH_2$;

$S(O)_2NH_2$;

C_{1-6} alkyl;

O-C_{1-6} alkyl;

$N(R^9)$-C_{1-6} alkyl;

COO-C_{1-6} alkyl;

OC(O)- C_{1-6} alkyl;

$C(O)N(R^{10})$- C_{1-6} alkyl;

$N(R^{11})$-C(O)-C_{1-6} alkyl;
$S(O)_2N(R^{12})$-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; or
$N(R^{13})S(O)_2$-C_{1-6} alkyl;

and wherein R^9, R^{10}, R^{11}; R^{12}, R^{13} are independently from each other H or C_{1-6} alkyl optionally substituted with one or more F;

Y is -O- or -$N(R^{14})$-;

R^{14}, T are independently from each other T^1-T^2 or T^2;

T^1 is selected from the group consisting of
-C_{1-6} alkyl-;
-C_{1-6} alkyl-O-; and
-C_{1-6} alkyl-$N(R^{15})$-;
wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^{15} is H or C_{1-6} alkyl, optionally substituted with one or more F;

T^2 is selected from the group consisting of
H;
phenyl;
wherein phenyl is optionally substituted with one, or independently from each other, more of
halogen;
CN;
R^{16};
COOH;
OH;
$C(O)NH_2$; or
$S(O)_2NH_2$;
C_{3-7} cycloalkyl; and
heterocycle;
wherein C_{3-7} cycloalkyl and heterocycle are optionally substituted with one, or independently from each other, more of

halogen;
CN;
R^{17};
OH;
=O, where the ring is at least partially saturated;
NH_2
COOH;
$C(O)NH_2$; or
$S(O)_2NH_2$;

R^{16} is selected from the group consisting of
C_{1-6} alkyl;
O-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{18})$- C_{1-6} alkyl;
$S(O)_2N(R^{19})$-C_{1-6} alkyl;
S(O)-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; and
$N(R^{20})S(O)_2$-C_{1-6} alkyl;
wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{21}$, $C(O)N(R^{22}R^{23})$, $S(O)_2N(R^{24}R^{25})$, OR^{26}, or $N(R^{27}R^{28})$;

R^{17} is selected from the group consisting of
C_{1-6} alkyl;
O-C_{1-6} alkyl;
$N(R^{18})$-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{19})$- C_{1-6} alkyl;
$N(R^{20})$-C(O)-C_{1-6} alkyl;
$S(O)_2N(R^{21})$-C_{1-6} alkyl;
S(O)-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; and

$N(R^{22})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{23}$, $C(O)N(R^{24}R^{25})$, $S(O)_2N(R^{26}R^{27})$, OR^{28}, or $N(R^{29}R^{30})$;

R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30} are independently from each other H or C_{1-6} alkyl.

Within the meaning of the present invention the terms are used as follows:

"Alkyl" means a straight-chain or branched carbon chain that may contain double or triple bonds. It is generally preferred that alkyl doesn't contain double or triple bonds. "C_{1-6} Alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. methyl, ethyl, $-CH=CH_2$, $-C\equiv CH$, n-propyl, isopropyl, $-CH=CH-CH_3$, $-CH_2-CH=CH_2$, n-butyl, isobutyl, $-CH=CH-CH_2-CH_3$, $-CH=CH-CH=CH_2$, sec-butyl tert-butyl, n-pentane, n-hexane, or amidst, e.g. $-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH(CH_3)-$, $-C(CH_2)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-CH(CH_3)_2-$. Each hydrogen of a C_{1-6} alkyl carbon may be replaced by a substituent.

"C_{3-7} Cycloalkyl" means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

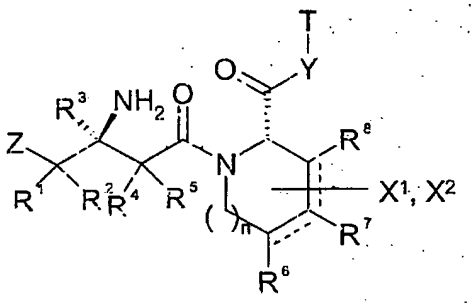
"Halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

"Heterocycle" means a cyclopentane, cyclohexane or cycloheptane ring that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one carbon atom up to 4 carbon atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, $-S(O)_2-$), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a heterocycle are furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran,

tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine.

"Heterobicycle" means a heterocycle which is condensed with phenyl or an additional heterocycle to form a bicyclic ring system. "Condensed" to form a bicyclic ring means that two rings are attached to each other by sharing two ring atoms. Examples for a heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, dihydroquinoline, isoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine.

A preferred stereochemistry of compounds according to the present invention is shown in formula (Ia)



(Ia)

Preferred compounds of formula (I) or (Ia) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formulas (I) or (Ia) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents R^1 - R^8, Z, n, X^1, X^2, Y and T of the formula (I) or (Ia) independently from each other have the following

meaning. Hence, one or more of the substituents R^1 - R^8, Z, n, X^1, X^2, Y and T can have the preferred or more preferred meanings given below.

Z is preferably phenyl or heterocycle and Z is optionally substituted independently from each other with 1, 2 or 3, preferably up to 2 of Cl, F, CN, or C_{1-6} alkyl.

Preferably, R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of H, F, OH and C_{1-6} alkyl.

It is preferred, that R^3 is H.

Preferably, n is 0 or 1, more preferably 1.

Preferably, X^1 and X^2 are independently from each other H or F.

It is preferred, that R^6 and R^7 form together a ring A and R^8 is H or F.

Preferably, A is selected from the group consisting of

phenyl;

wherein phenyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

COOH;

OH;

$C(O)NH_2$;

$S(O)_2NH_2$;

C_{1-6} alkyl;

O-C_{1-6} alkyl;

COO-C_{1-6} alkyl;

OC(O)- C_{1-6} alkyl;

C(O)NH- C_{1-6} alkyl;

$S(O)_2$NH-C_{1-6} alkyl;

$S(O)_2$-C_{1-6} alkyl; or

$NHS(O)_2$-C_{1-6} alkyl;

and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;

NH_2

COOH;

$C(O)NH_2$;

$S(O)_2NH_2$;

C_{1-6} alkyl;

O-C_{1-6} alkyl;

NH-C_{1-6} alkyl;

COO-C_{1-6} alkyl;

OC(O)- C_{1-6} alkyl;

C(O)NH- C_{1-6} alkyl;

NH-C(O)-C_{1-6} alkyl;

$S(O)_2$NH-C_{1-6} alkyl;

$S(O)_2$-C_{1-6} alkyl; or

$NHS(O)_2$-C_{1-6} alkyl;

Y is preferably -N(R^{31})- and R^{31} is H or C_{1-4} alkyl, more preferably H or methyl, most preferably H.

T is preferably T^2 and T^2 is H.

In embodiments T is preferably T^2 and T^2 is C_{3-7} cycloalkyl, preferably cyclopropyl or cyclobutyl, more preferably cyclopropyl, whereby cycloalkyl may be substituted with 1 or 2, preferably 1, of halogen; CN; OH; NH_2 COOH; $C(O)NH_2$; or $S(O)_2NH_2$, more preferably COOH or $C(O)NH_2$.

Preferably, T^1 is C_{1-6} alkyl.

It is preferred, that T^2 is selected from the group consisting of

phenyl;

wherein phenyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

COOH;

OH;

$C(O)NH_2$; or

$S(O)_2NH_2$;

and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;

NH_2

COOH;

$C(O)NH_2$; or

$S(O)_2NH_2$.

In one embodiment, T^2 is preferably heterocycle, whereby heterocycle may be substituted with 1-3, preferably 1 or 2, substituents selected from halogen, CN, O-C_{1-4} alkyl, C_{1-4} alkyl or $S(O)_2CH_3$; preferably, the heterocycle is aromatic, more preferably containing 1 or 2 heteroatoms selected from N and O, most preferably N. Particularly preferred is pyridyl.

In one embodiment, T^1-T^2 is preferably $S(O)_2$-C_{1-4} alkyl, preferably $S(O)_2$-methyl.

The following definitions for Y-T are also preferred:

- Y-T is NH-T and T is T^1-T^2. In this case, T^1-T^2 is preferably a group as defined below.

In one embodiment, T^1-T^2 is preferably CH_2-phenyl, whereby phenyl may be substituted with 1-3, preferably 1 or 2, substituents selected from halogen, CN, O-C_{1-4} alkyl, C_{1-4} alkyl or $S(O)_2CH_3$, preferably phenyl is unsubstituted or substituted by 1, 2 or 3 halogen, such as F.

In one embodiment, T^1-T^2 is preferably CH_2-heterocycle, whereby heterocycle may be substituted with 1-3, preferably 1 or 2, substituents selected from halogen, CN, O-C_{1-4} alkyl, C_{1-4} alkyl or $S(O)_2CH_3$; preferably, the heterocycle is aromatic, more preferably containing 1 or 2 heteroatoms selected from N and O, most preferably N.

In one embodiment, T^1-T^2 is preferably CH_2-C_{3-7} cycloalkyl, preferably CH_2-cyclopropyl or CH_2-cyclobutyl, more preferably CH_2-cyclopropyl, whereby cycloalkyl may be substituted with 1 or 2, preferably 1, of halogen; CN; OH; NH_2 COOH; $C(O)NH_2$; or $S(O)_2NH_2$, more preferably COOH or $C(O)NH_2$.

In one embodiment, T^1-T^2 is preferably C_{1-4} alkyl, preferably methyl or ethyl, whereby methyl may be substituted with 1 or 2 F and ethyl may be substituted with 1 to 4, preferably 3, F. Examples of substituted C_{1-4} alkyl include CHF_2, CH_2CHF_2, CH_2CF_3, CF_2CH_3 or $CH_2CH_2CF_3$.

In one embodiment, T^1-T^2 is preferably C_{1-4} alkyl-OH, preferably CH_2-OH, CH_2CH_2-OH or $CH_2CH_2CH_2$-OH.

In one embodiment, T^1-T^2 is preferably C_{1-4} alkyl-O-C_{1-4} alkyl, preferably CH_2-O-CH_3, CH_2CH_2-O-CH_3 or CH_2CH_2-O-CH_2CH_3.

In one embodiment, T^1-T^2 is preferably $S(O)_2$-C_{1-4} alkyl, preferably $S(O)_2$-methyl.

Y-T is NH-T and T is T^2. In this case, T^2 is preferably a group as defined below.

In one embodiment, T^2 is preferably H.

In one embodiment, T^2 is preferably C_{3-7} cycloalkyl, preferably cyclopropyl or cyclobutyl, more preferably cyclopropyl, whereby cycloalkyl may be substituted with 1 or 2, preferably 1, of halogen; CN; OH; NH_2 COOH; $C(O)NH_2$; or $S(O)_2NH_2$, more preferably COOH or $C(O)NH_2$.

In one embodiment, T^2 is preferably heterocycle, whereby heterocycle may be substituted with 1-3, preferably 1 or 2, substituents selected from halogen, CN, O-C_{1-4} alkyl, C_{1-4} alkyl or $S(O)_2CH_3$; preferably, the heterocycle is aromatic, more preferably

containing 1 or 2 heteroatoms selected from N and O, most preferably N. Particularly preferred is pyridyl.
In one embodiment, T^2 is preferably heterocycle, more preferably an aromatic heterocycle, containing preferably 1 to 4 N, such as tetrazolyl.

- Y-T is $N(C_{1-4}$ alkyl)-T, preferably N(methyl)-T, and T is T^2. In this case, T^2 is preferably a group as defined below.

In one embodiment, T^2 is preferably C_{1-4} alkyl, preferably methyl or ethyl, whereby methyl may be substituted with 1 or 2 F and ethyl may be substituted with 1 to 4, preferably 3, F.
In one embodiment, T^2 is preferably C_{3-7} cycloalkyl, preferably cyclopropyl or cyclobutyl, more preferably cyclopropyl, whereby cycloalkyl may be substituted with 1 or 2, preferably 1, of halogen; CN; OH; NH_2 COOH; $C(O)NH_2$; or $S(O)_2NH_2$, more preferably COOH or $C(O)NH_2$.

- Y-T is O-T and T is T^2. In this case, T^2 is preferably a group as defined below.

In one embodiment, T^2 is preferably H.
In one embodiment, T^2 is preferably C_{1-4} alkyl, preferably methyl or ethyl, whereby methyl may be substituted with 1 or 2 F and ethyl may be substituted with 1 to 4, preferably 3, F.

In the case that Y contains the group R^{14}, the following is preferred in embodiments:
When R^{14} is T^1-T^2 and represents $-C_{1-6}$ alkyl and T is T^1-T^2 and represents $-C_{1-6}$ alkyl, C_{1-6} alkyl-O- or $-C_{1-6}$ alkyl-$N(R^{15})$-, then R^{14} and T may form together a 3 to 7 membered cyclic group, preferably a 5 or 6 membered cyclic group, which contains 1 N and optionally 1 further O or N, whereby this cyclic group may be further substituted. Examples of the cyclic group include piperidino, piperazine and morpholino. Preferred substituents on the cyclic group include $C(O)$-C_{1-4} alkyl, preferably C(O)-Me and $S(O)_2$-C_{1-4} alkyl, preferably $S(O)_2$-Me.

The following embodiments are preferred for A:

In a first embodiment, A is C_{3-7} cycloalkyl which is as defined above.

In a second embodiment A is phenyl which is as defined above. In this embodiment, Y-T are preferably together

NH_2;

(NH)-C_{1-6} alkyl-C_{3-7} cycloalkyl;

(NH)-C_{3-7} cycloalkyl; or

(NH)-phenyl; wherein in the definition of Y-T

phenyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

COOH;

OH;

$C(O)NH_2$; or

$S(O)_2NH_2$;

and

cycloalkyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

O, where the ring is at least partially saturated;

NH_2

COOH;

$C(O)NH_2$; or

$S(O)_2NH_2$.

When A is phenyl, this ring is preferably formed by R^8 and R^7.

When A is phenyl, then Y-T are preferably together

(NH)-C_{1-6} alkyl-phenyl; wherein in the definition of Y-T phenyl is unsubstituted.

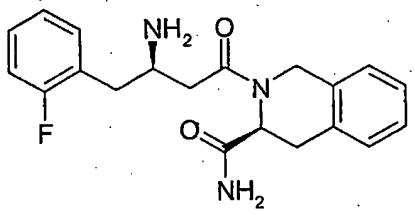
In a third embodiment A is heterocycle which is as defined above.

When A is heterocycle, this ring is preferably formed by R^8 and R^7. When R^6 and R^7 form a ring A, it is preferably not an aromatic heterocycle.

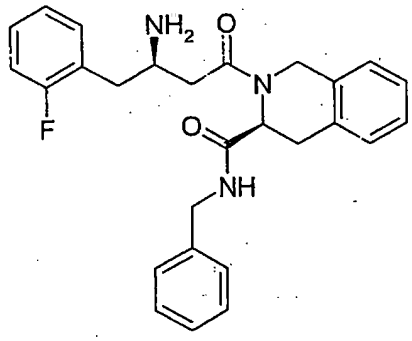
When A is heterocycle, it is in one embodiment a non-aromatic ring which is fully or partially saturated or unsaturated. In one embodiment, it is selected from furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyrimidine, piperazine.

Compounds of the formula (I) or (Ia) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

Preferred embodiments of the compounds according to present invention are shown in formula (IIa) to (IIe).



(IIa)



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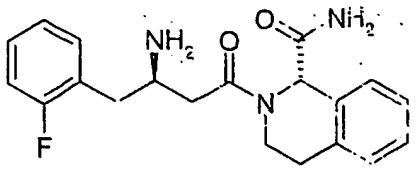
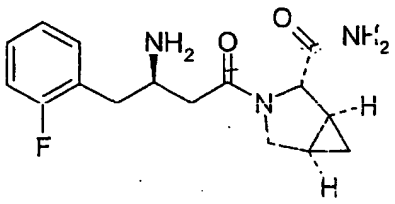
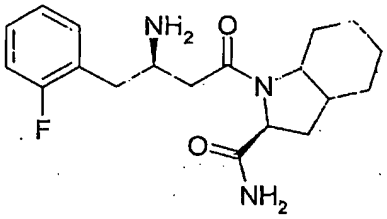


(IIc)

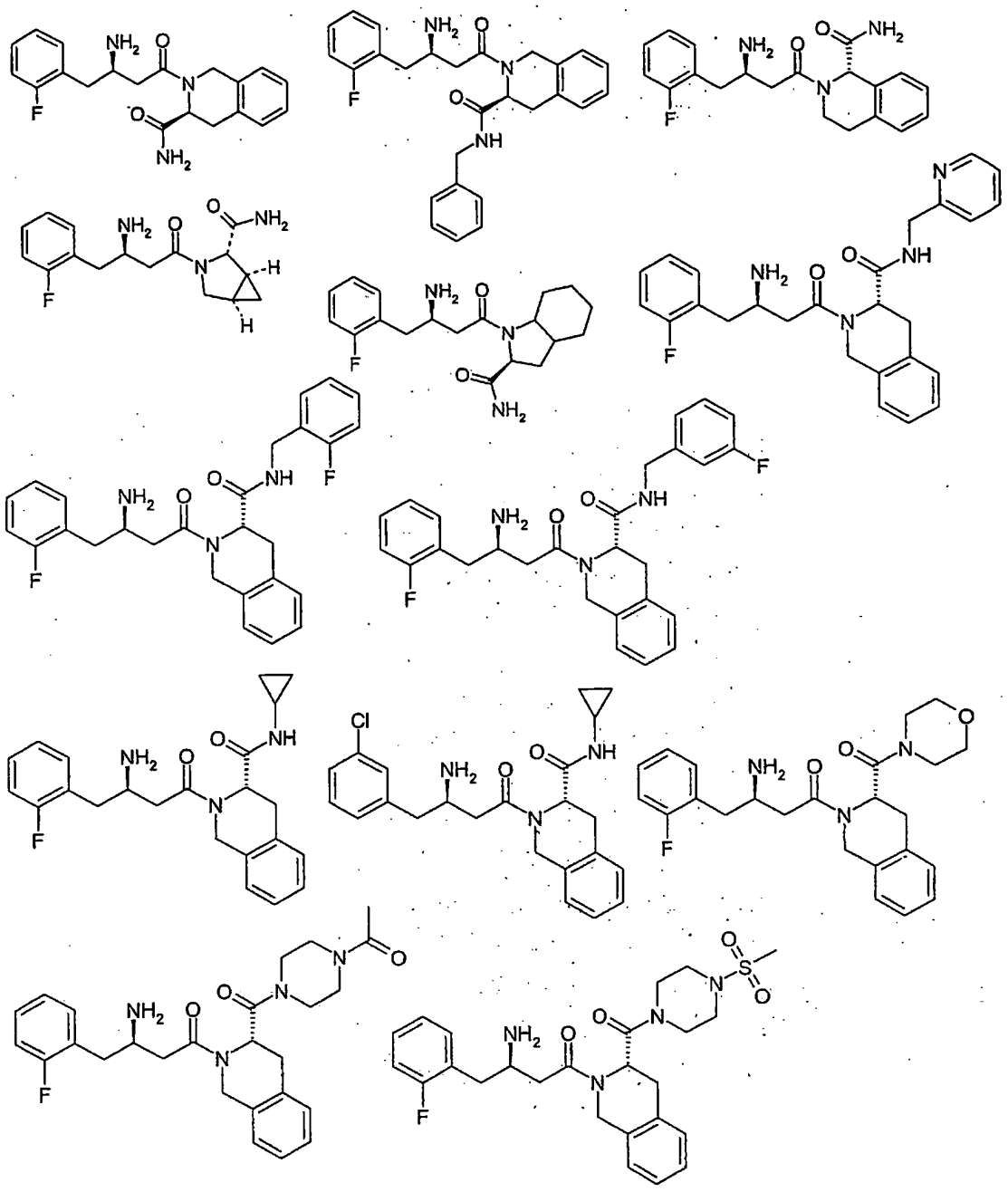


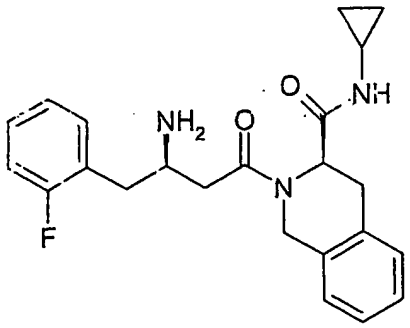
(IId)

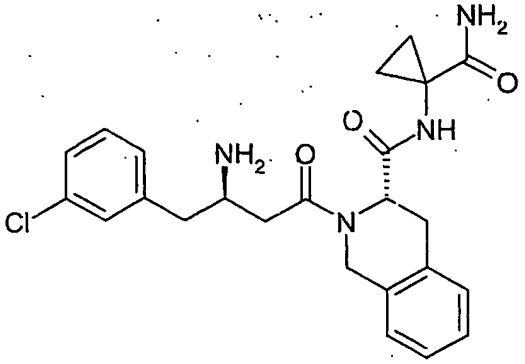


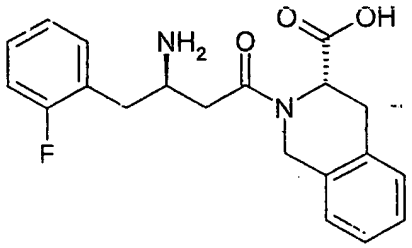
(IIe)

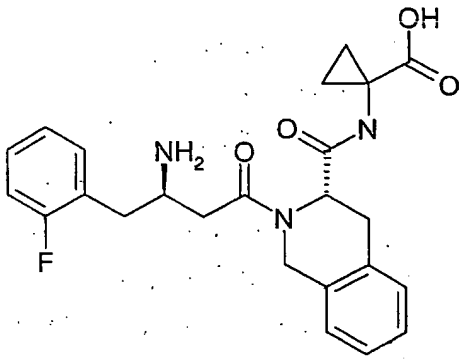
The following compounds are also preferred:

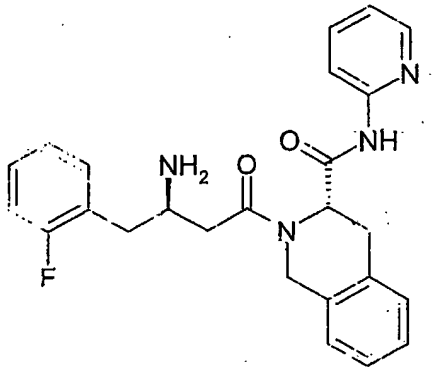


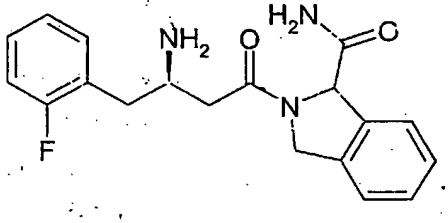


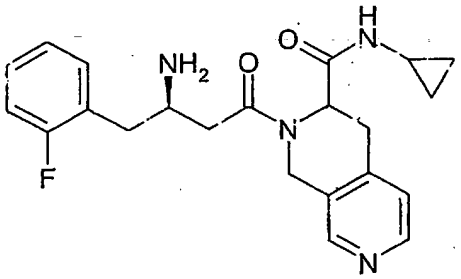


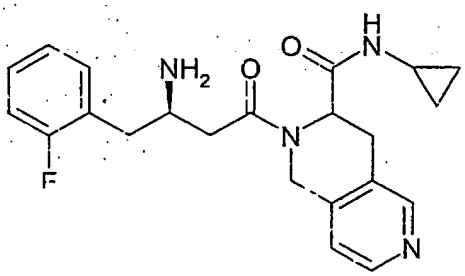


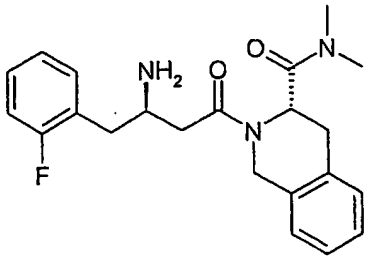


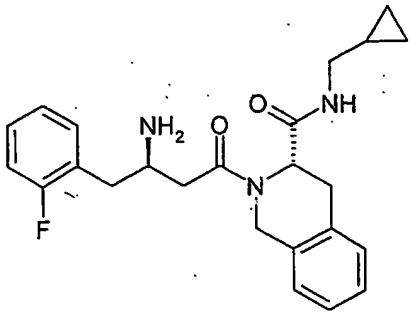


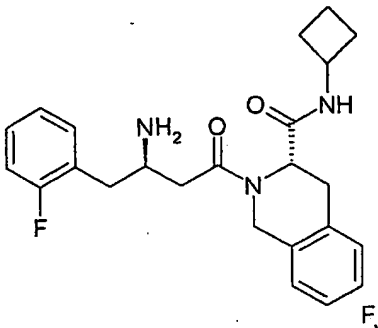


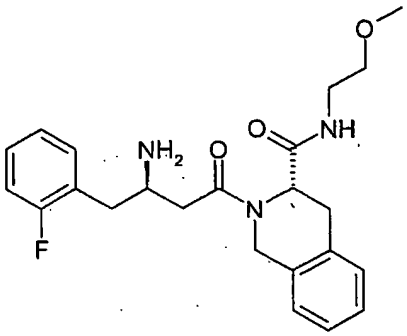


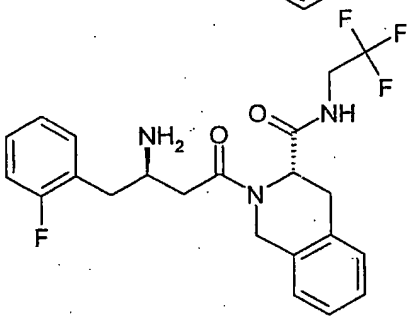


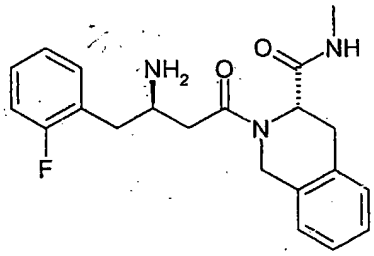


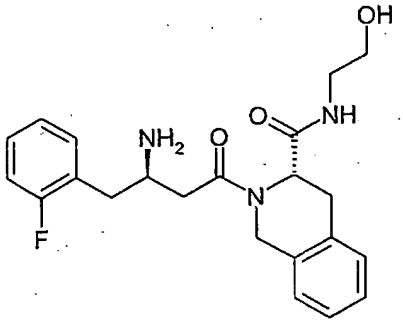


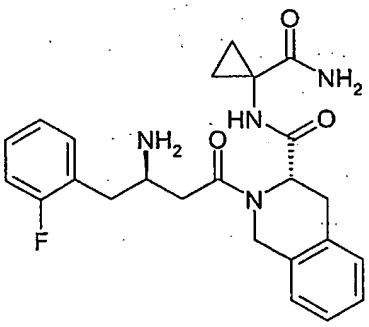


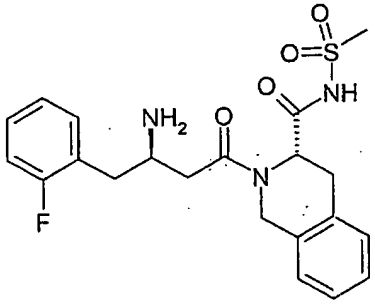


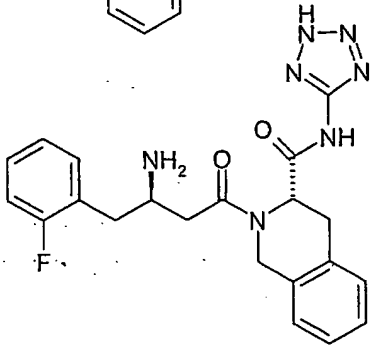












Furthermore, the present invention provides prodrug compounds of the compounds of the invention as described above.

"Prodrug compound" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Metabolites of compounds of formula (I) or (Ia) are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) or (Ia) or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are claimed separately and together as mixtures in any ratio. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) or (Ia) may be obtained from stereoselective synthesis using optically pure starting materials.

In case the compounds according to formula (I) or (Ia) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) or (Ia) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise

examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) or (Ia) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) or (Ia) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) or (Ia) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) or (Ia) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention provides compounds of general formula (I) or (Ia) or their prodrugs as DPP-IV inhibitors. DPP-IV is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DPP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes.

DPP-IV related diseases are described in more detail in WO-A-03/181 under the paragraph "Utilities" which is herewith incorporated by reference.

Accordingly, the present invention provides compounds of formula (I) or (Ia) or their prodrugs or pharmaceutically acceptable salt thereof for use as a medicament.

Furthermore, the present invention provides the use of compounds of formula (I) or (Ia) or their prodrugs or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholestrerolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; anxiety; depression; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; ist sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency. Preferred is non-insulin dependent (Type II) diabetes mellitus and obesity.

The present invention provides pharmaceutical compositions comprising a compound of formula (I) or (Ia), or a prodrug compound thereof, or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

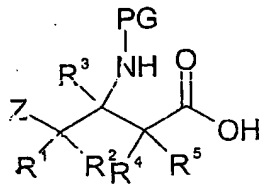
A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients like one or more additional compounds of formula (I) or (Ia), or a prodrug compound or other DPP-IV inhibitors.
Other active ingredients are disclosed in WO-A-03/181 under the paragraph "Combination Therapy" which is herewith incorporated by reference.
Accordingly, other active ingredients may be insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-lB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; a-glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinyl alcohol; nicotinic acid or a salt thereof; PPARa agonists; PPARoly dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPARo agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; or anti-inflammatory agents or pharmaceutically acceptable salts of these active compounds.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids.

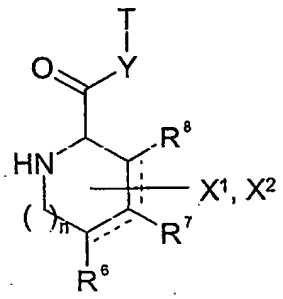
The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of formula (I) or (Ia) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols,

The compounds of formula (I) of the present invention can be prepared from beta amino acid intermediates such as those of formula (III) and substituted amine intermediates such as those of formula (IV), using standard peptide coupling conditions. The preparation of these intermediates is described in the following schemes.



(III)



(IV)

Some abbreviations that may appear in this application are as follows:

ABBREVIATIONS

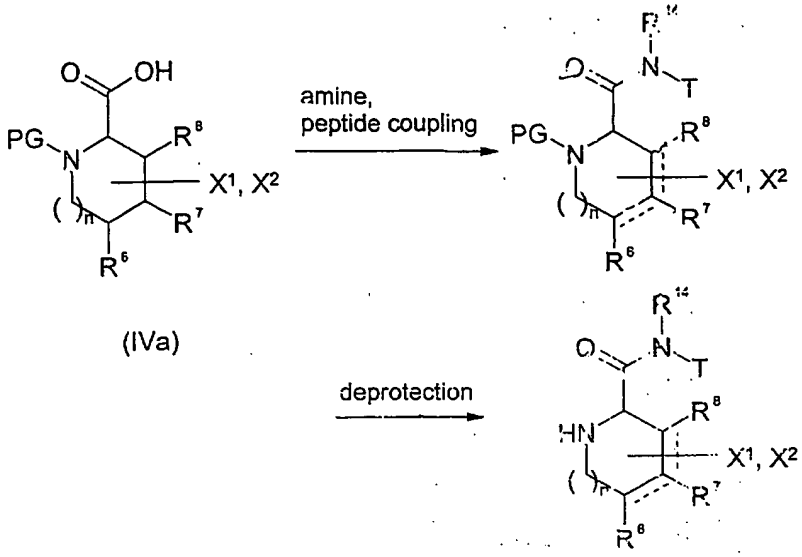
Designation	
bs	Broad singlet
Boc (or BOC)	*tert*-Butoxycarbonyl
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N	Triethylamine
Fmoc	9-Fluorenylmethoxycarbonyl
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
PG	Protecting group
rt	Retention time
^{t}BuOH	*tert*-Butanol
TFA	Trifluoroacetic acid

Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Beta amino acids intermediates carrying a suitable protecting group (PG) may be commercially available, known in the literature or may be conveniently synthesized by a variety of methods familiar to those skilled in the art. Routes to these type of compounds are reviewed in Cole, *Tetrahedron*, 32, 9517 (1994), Juaristi et al., *Aldrichchimica Acta*, 27, 3 (1994) and Juaristi, Enantioselective Synthesis of β-Amino Acids, Ed. Wiley-VCH, New York, 1997.
In particular, 3-amino-4-(2,4,5-trifluoro-phenyl)-butyric acid may be synthesized by a variety of methods as reported in the patent applications WO 2004069162, WO 2004064778, WO 2004037169, WO 2004032836 and in the articles *JACS*, 126, 3048 (2004) and *JACS*, 126, 9918 (2004).

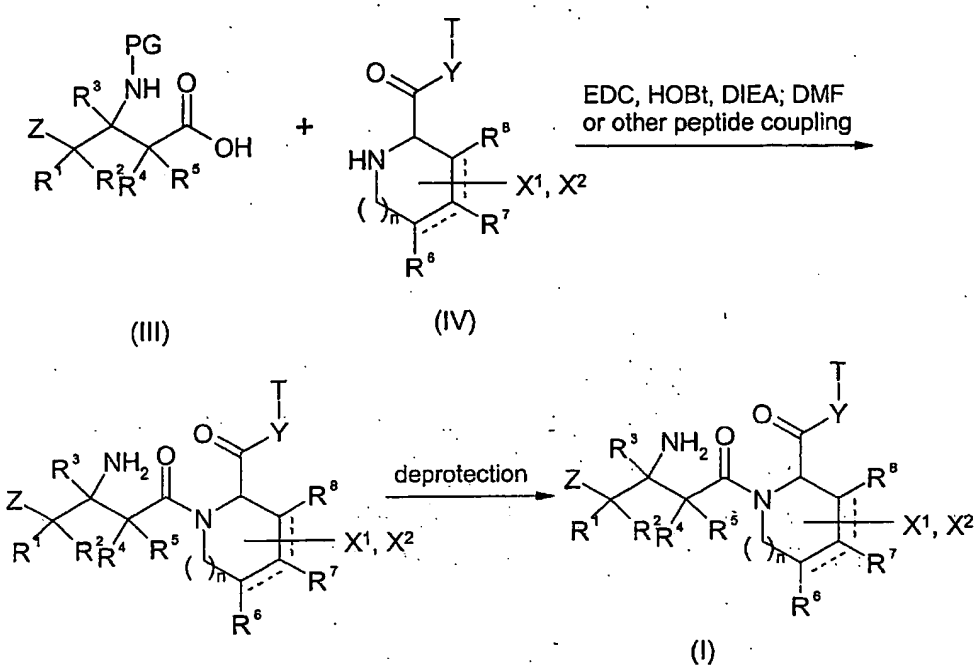
Compounds of formula (IV) may be purchased from commercially available sources or may be synthesized by one skilled in the art. Scheme A exemplarily illustrates a route for the synthesis of intermediates (IV) where the residue -Y-T is -N(R^{14}T). A suitably protected acid (IVa), commercially available or synthesized by familiar methods, is employed in a standard peptide coupling reaction. For example, coupling can be performed with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIEA) in *N,N*-dimethylformamide (DMF) or another suitable solvent. The protection group is removed utilizing methods as described in the literature such as treatment with trifluoroacetic acid in case of Boc. In some cases the coupling products may be further modified by manipulation of substituents on -NR^{14}T. These manipulations may include, but are not limited to, hydrolysis, acylation, alkylation, reduction, oxidation and other reactions which are known to those skilled in the art.

Scheme A



Compounds of formula I may be prepared by coupling of the intermediates of formulas (III) and (IV) under standard peptide coupling conditions, reagents and protecting groups and subsequent removal of the protecting group as depicted exemplarily for compounds of the formula (I) in scheme B. As outlined above, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIEA) may be used in the coupling, whereas the removal of the protection group can be performed, for example, with trifluoroacetic acid in the case of Boc.

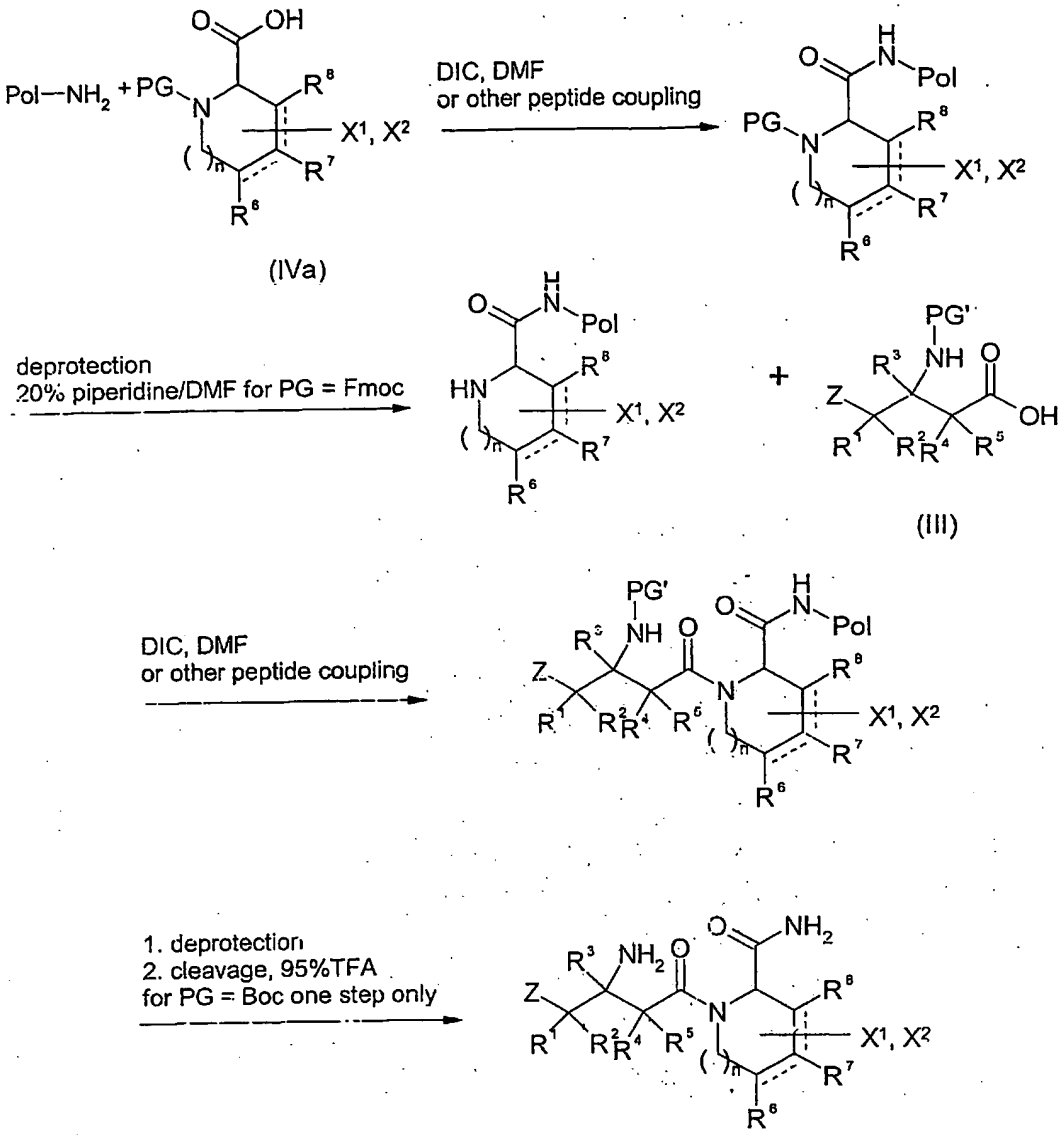
Scheme B



Coupling products may, in some cases, be further modified by manipulation of substituents on Y-T. These manipulations may include, but are not limited to, hydrolysis, acylation, alkylation, reduction, oxidation and other reactions which are known to those skilled in the art.

Alternatively, for compounds with -Y-T = $-NH_2$ a route that is illustrated in scheme C may be particularly applicable. A suitably protected, Fmoc for example, acid (IVa) is coupled to Rink amide resin (Pol) under standard conditions. The protecting group is removed with 20% piperidine in DMF in the case of Fmoc, for example, and the resulting amine treated with intermediate (III) under peptide coupling conditions. For the example PG' = Boc deprotection and cleavage from the resin are achieved conveniently in one step to give the primary amide.

Scheme C



For the purification of intermediates or final products, flash chromatography on silica gel may be suitable for the free amines whereas the use of preparative HPLC leads to the isolation of the corresponding trifluoroacetic acid salts or formate salts.

Compounds may be prepared by other means however, and the suggested starting materials and procedures described below are exemplary only and should not be considered as limiting the scope of the invention.

Unless otherwise noted, all non-aqueous reactions were carried out under argon atmosphere with commercial dry solvents. Compounds were purified using flash column chromatography using Merck silica gel 60 (230-400 mesh) or reverse phase preparative HPLC using a Reprosil-Pur ODS3, 5 µm, 20 x 125 mm column with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The ^{1}H-NMR spectra were recorded on a Varian VXR-S (300 MHz for ^{1}H-NMR) using d_6-dimethylsulfoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LC/MS was performed using Reprosil-Pur ODS3, 5 µM, 1 x 60 mm columns with a linear gradient from 5% to 95% acetonitrile in water (0.1% TFA or formic acid) at a flow rate of 250 µL/min; retention times are given in minutes. Methods are:

(I) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214, 254 and 275 nm, 10 min. linear gradient; (II) idem but 5 min. linear gradient; (III) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, 10 min. linear gradient; (IV) idem but 5 min. linear gradient; (V) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, 8 min. with a linear gradient from 10% to 60% acetonitrile in water (0.1% TFA or formic acid), then 4 min at 99%; (VI) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, 8 min. with a linear gradient from 1% to 30% acetonitrile in water (0.1% TFA or formic acid), then 4 min at 99%.

Analytical chiral separation was performed on a DAICEL Chiralpak AD-H 4.6mm x 250mm with a linear gradient from 50% to 5% heptane in ethanol (0.1% DEA) at a flow rate of 0.7 mL/min. The analytical chiral runs are performed by T = 22°C and p=112 bar (ca. 20 bars postcolumn from MS ESI-capillary.

The LC/MS system was equipped in the standard analytical set-up, i.e. 2 pumps, mixer and 2µl sample-loop at the injector. Post-column, the semi-micro UV-cell was used and then a ca. 1:2 splitter to achieve a flow to the MS of appr. 300-400 µl/min (ESI+).

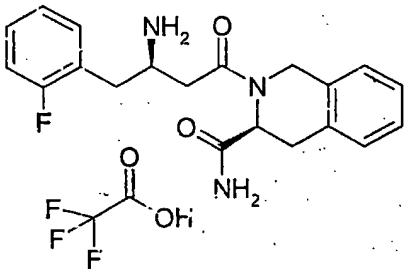
Preparative chiral separation was performed on a DAICEL Chiralpak AD-H 20mm x 250mm plus guard-column AD-H 10 mm X 20 mm with a linear gradient from 50% to 5% heptane in ethanol (0.1% DEA) at a flow rate of 7 mL/min.

EXAMPLES

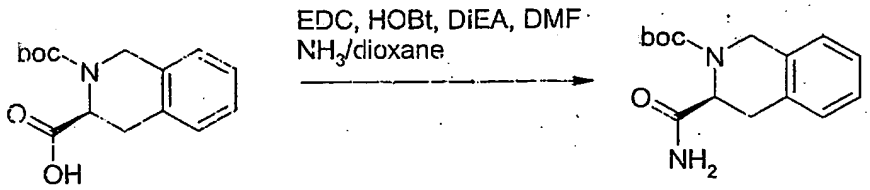
The following examples show representative compounds and their synthesis. However, they are for purposes of illustration only and should not be construed as limiting the invention in any way.

PREPARATIONS

Example 1



Step 1

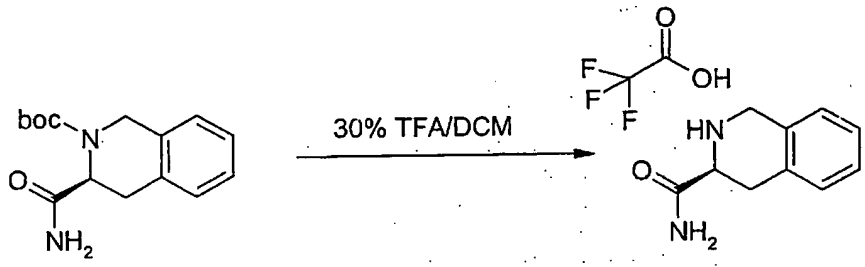


(3*S*)-3-Carbamoyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

A mixture of 40 mg (0.14 mmol) (S)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 31 mg (0.16 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 22 mg (0.16 mmol) 1-hydroxybenzotriazole (HOBt) and 50 µL (0.28 mmol) diisopropylethylamine (DIEA) in 3 mL *N,N*-dimethylformamide is stirred at room temperature for 10 min before 1 mL (0.5

mmol) of a solution of ammonia in dioxane (0.5M) is added and stirring continued overnight. The solution is diluted with 50 mL ethyl acetate, washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution, and brine and dried over sodium sulphate. The solvent is removed under vacuum to give the title compound.
LCMS (II) rt 2.37, m/z 340 $(M+Na+CH_3CN)^+$.

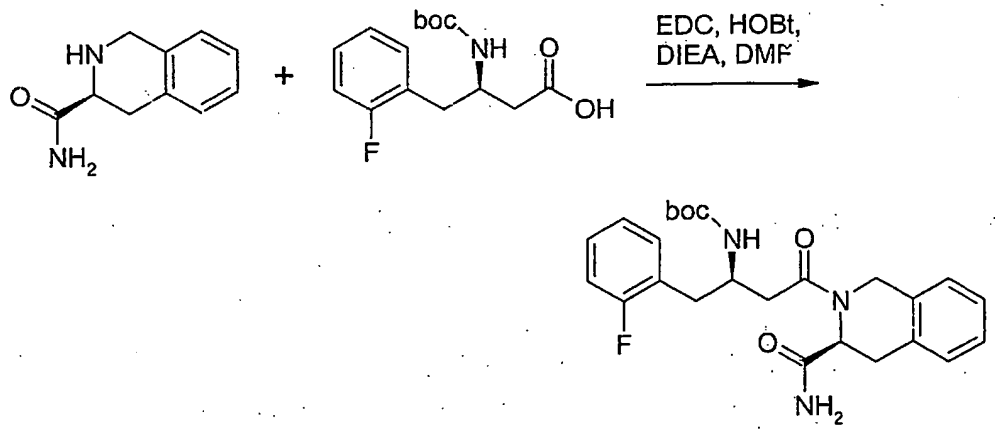
Step 2



1,2,3,4-Tetrahydro-isoquinoline-(3*S*)-3-carboxylic acide amide, trifluoroacetate salt

30 mg (0.11 mmol) of the product from step 1 are dissolved in 1 mL of dichloromethane and 0.5 mL of trifluoroacetic acid are added. The solution is stirred for 30 min at room temperature and the solvents removed under reduced pressure. The crude material is taken directly to the next step.
LCMS (IV) rt 1.53, m/z 218 $(M+H+CH_3CN)^+$.

Step 3

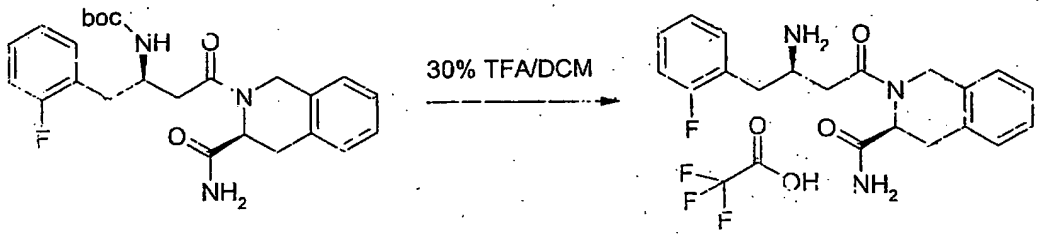


[3-((3*R*)-3-Carbamoyl-3,4-dihydro-1H-isoquinoline-2-yl)-1-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid tert-butyl ester

To a solution of 25 mg (0.085 mmol) Boc-(R)-3-amino-4-(2-fluorophenyl)-butyric acid in 1 mL *N,N*-dimethylformamide is added 18 mg (0.094 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 15 mg (0.094 mmol) 1-hydroxybenzotriazole (HOBt) and 57 µL (0.33 mmol) diisopropylethylamine (DIEA) and after 5 min the crude material from step 2 (0.11 mmol) dissolved in 1 mL *N,N*-dimethylformamide. The mixture is stirred overnight at room temperature and diluted with ethyl acetate. The organic phase is washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution, and brine, dried over sodium sulphate and concentrated under vacuum. Purification by flash chromatography (silica gel, cyclohexane to ethyl acetate) affords the title compound.

LCMS (II) rt 2.77, m/z 478 $(M+Na)^+$.

Step 4



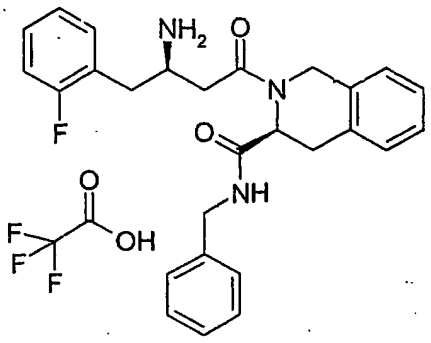
2-[(3*R*)-3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-(3*S*)-3-carboxylic amide, trifluoroacetate salt

30 mg (0.066 mmol) of the product from step 3 are dissolved in 2 mL dichloromethane and 1 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min and the solvent evaporated under vacuum. Filtration through a short plug of silica gel (dichloromethane to 5 % methanol in dichloromethane) affords the title compound.

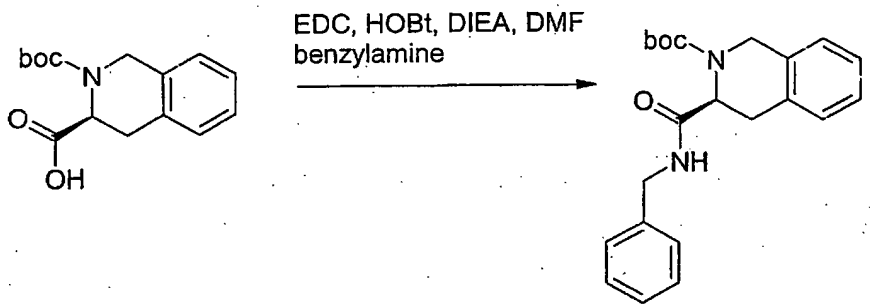
LCMS (IV) rt 2.77, m/z 356 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.68 - 3.20 (m, 4H), 3.69 - 3.85 (m, 2H), 4.37 – 4.69 (m, 3H), 4.93 (m, 1H), 6.86 (bs, 1H), 7.05 - 7.49 (m, 8H), 7.86 (bs, 4H).

Example 2



Step 1

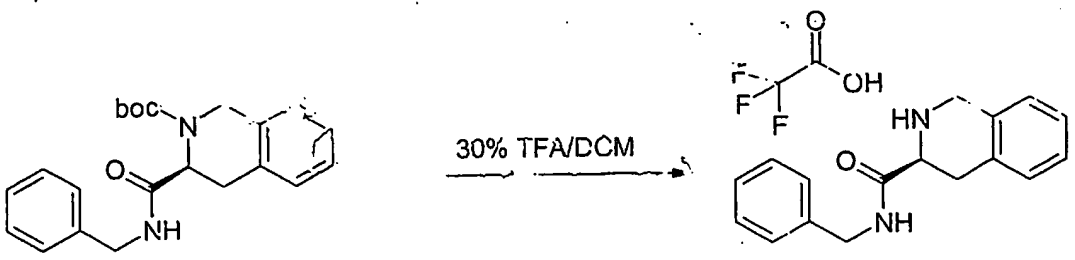


(3*S*)-3-Benzylcarbamoyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tertbutyl ester

A mixture of 100 mg (0.34 mmol) (*S*)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 71 mg (0.37 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 59 mg (0.43 mmol) 1-hydroxybenzotriazole (HOBt) and 228 µL (1.31 mmol) diisopropylethylamine (DIEA) in 5 mL *N,N*-dimethylformamide is stirred at room temperature for 10 min before 73 µL (0.67 mmol) benzylamine are added and stirring continued overnight. The solution is diluted with 50 mL ethyl acetate, washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution, and brine and dried over sodium sulphate. The solvent is removed under vacuum and the crude material purified by flash chromatography (silica gel, cyclohexane to 30% ethyl acetate in cyclohexane) to afford the title compound.

LCMS (IV) rt 2.95, m/z 308 $(M+H\text{-}boc+CH_3CN)^+$.

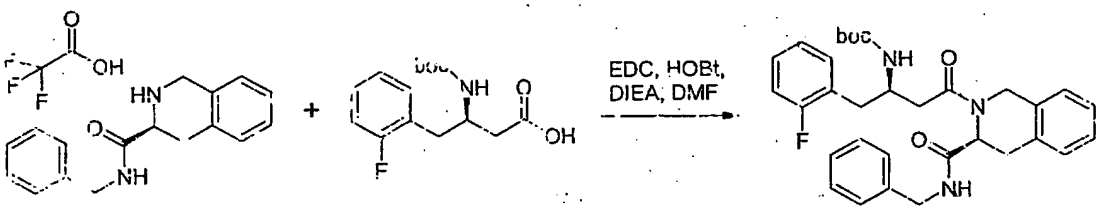
Step 2



(3S)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid benzylamide, trifluoroacetate salt

The title compound is prepared according the procedure in step 2 from example 1 and taken directly to the next step.

Step 3

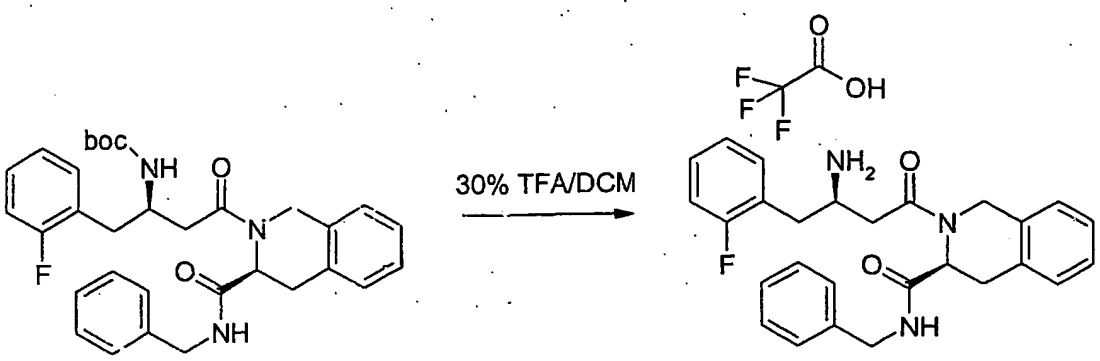


[3-((3S)-3-Benzylcarbamoyl-3,4-dihydro-1H-isoquinolin-2-yl)-1-(2-fluoro-benzyl)-3-oxo-propyl]carbamic acid tert-butyl ester

Obtained from the material from step 2 employing the procedure of step 3 for example 1.

LCMS (II) rt 3.28, m/z 546 $(M+H)^+$.

Step 4



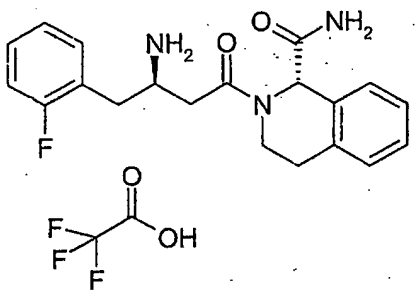
2-[(3R)-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-(3*S*)-3-carboxylic acid benzylamide, trifluoroacetate salt

The title compound is prepared from the material of step 3 following the procedure for step 4 outlined for example 1.

LCMS (II) rt 2.38, m/z 446 $(M+H)^+$.

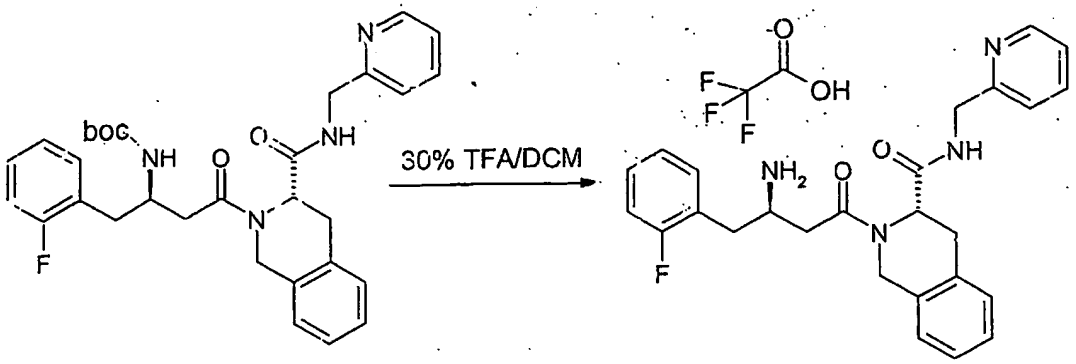
^{1}H-NMR in part (300 MHz, DMSO-d_6) δ = 2.74 - 3.15 (m, 5H), 3.24 (dd, J = 3.5 Hz, J = 15.5 Hz, 1H), 3.78 (m, 1H), 3.98 (dd, J = 5.5 Hz, J = 16.0 Hz, 1H), 4.24 (dd, J = 5.9 Hz, J = 15.6 Hz, 1H), 4.57 (m, 2H), 4.99 (dd, J = 3.8 Hz, J = 5.7 Hz, 1H), 6.66 – 6.72 (m, 2H), 7.06 - 7 40 (m, 11H), 7.86 (bs, 3H), 8.12 (t, J = 6.0 Hz, 1H).

Example 3



2-[(3*R*)-3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-(1*S*)-1-carboxylic acid amide, trifluoroacetate salt

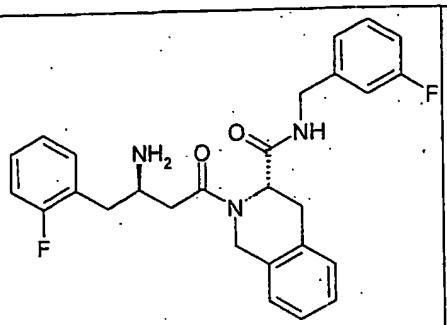
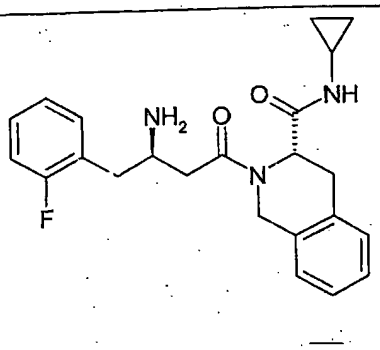
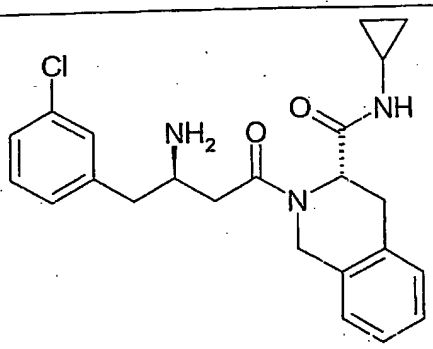
40 mg Rink Amide Novagel (loading 0.6 mmol/g – 0.024 mmol) are briefly swollen in *N,N*-dimethylformamide and drained. A solution of 42 mg (0.11 mmol) Fmoc-L-tetrahydroisoquinoline-1-carboxylic acid and 21 µL (0.15 mmol) diisopropylcarbodiimide

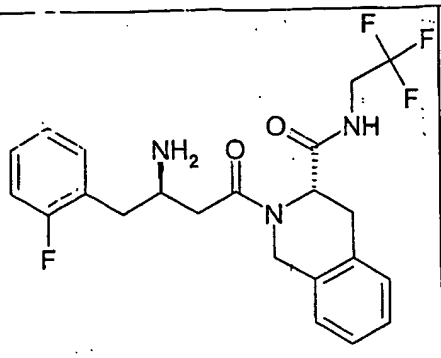
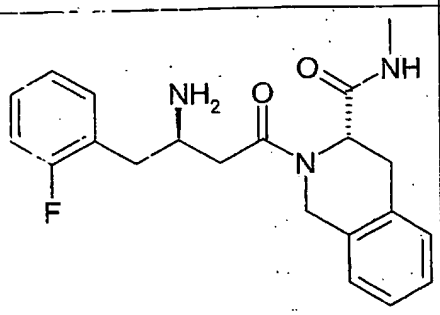
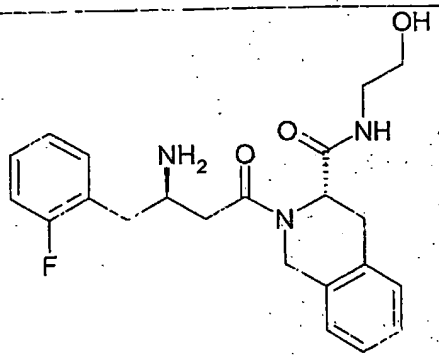


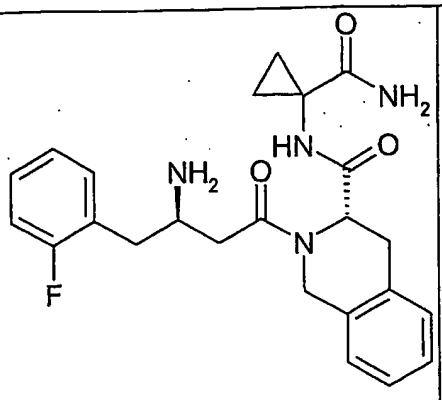
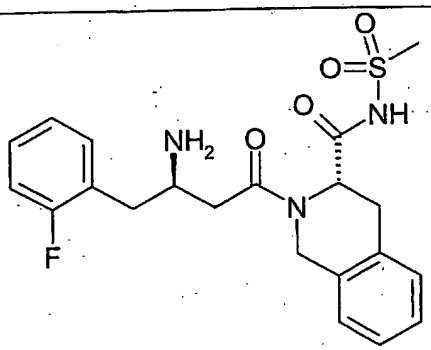
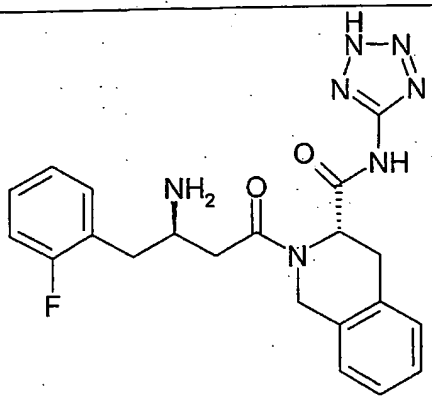
2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (pyridin-2-ylmethyl)-amide, trifluoroacetate salt

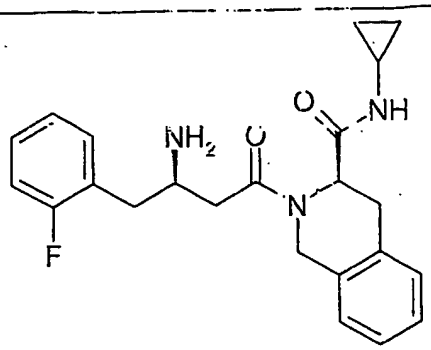
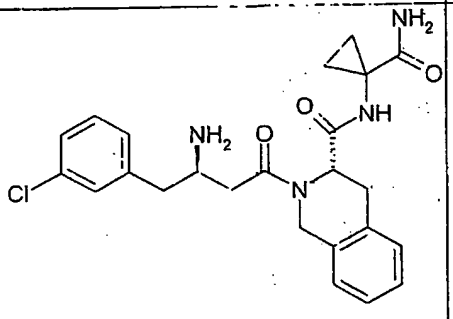
21 mg (0.039 mmol) of the product from step 3 are dissolved in 1 mL dichloromethane and 0.5 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min and the solvent evaporated under vacuum. Filtration through a short plug of silica gel (dichloromethane to 5% methanol in dichloromethane) yields the title compound.

LCMS (II) rt 1.73, m/z 447 $(M+H)^+$.

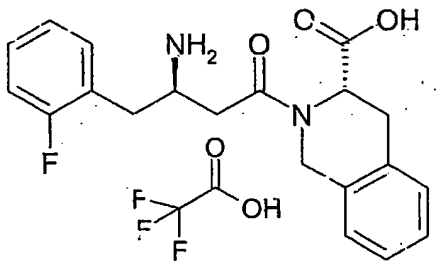
8		(IV) rt 2.43, m/z 464 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.72 - 3.34 (m, 6H), 2H overlap with the water peak, 4.19 – 4.35 (m, 1H), 4.50 – 4.61 (m, 2H), 4.68 – 4.75 and 4.93-5.00 (2m, 1H), 6.48 - 6.60 (m, 2H), 6.85 – 6.97 (m, 1H), 7.06 – 7.41 (m, 9H), 7.90 (bs, 3H), 8.13 - 8.21 (m, 0.7 H), 8.31 - 8.38 (m, 0.3H).
9		(IV) rt 2.14, m/z 397 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.15-0.28 (m, 2H), 0.47 - 0.57 (m, 2H), 2.37 - 2.46 (m, 1H), 2.66 - 3.11 (m, 6H), 3.65 - 3.83 (m, 1H), 4.35 – 4.68 (m, 2H), 4.80 – 4.83 (m, 1H), 7.07 - 7.20 (m, 6H), 7.26 – 7.38 (m, 2H), 7.67 - 7.98 (m, 3H).
10		(IV) rt 2.14, m/z 412 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.18 - 0.28 (m, 2H), 0.48 - 0.59 (m, 2H), 2.37-2.52 (m, 1H), 2.68 - 3.13 (m, 6H), 1H overlaps with the water peak, 4.36 – 4.73 (m, 2H), 4.78 – 4.82 (m, 1H), 7.11 - 7.19 (m, 4H), 7.23 – 7.39 (m, 4H), 7.69 - 7.88 (m, 4H).

18		(IV) rt 2.23, m/z 438 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.70 - 3.18 (m, 6H), 3.65 - 3.80 (m, 3H) 4.39 – 4.70 (m, 2H), 4.92 – 4.95 (m, 1H), 7.08 - 7.20 (m, 6H), 7.25 – 7.38 (m, 2H), 7.88 (bs, 3H), 8.32 - 8.36 (m, 0.8H), 8.51 - 8.57 (m, 0.2H).
19		(IV) rt 1.94, m/z 370 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.39 (d, 3H), 2.66 - 3.24 (m, 6H), 3.68 - 3.84 (m, 1H), 4.09 - 4.22 (m, 2H), 4.64 - 4.74 (m, 2H), 4.90 - 4.93 (m, 1H), 7.08-7.40 (m, 8H), 7.57 – 7.65 (m, 0.8 H), 7.74 - 7.96 (m, 3.2H).
20		(II) rt 2.08, m/z 426 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.77 - 3.37 (m, 8H), 3.66 - 3.84 (m, 1H), 4.09-4.22 (m, 2H), 4.36 – 4.70 (m, 3H), 4.84 – 4.91 (m, 1H), 7.08-7.20 (m, 6H), 7.23 – 7.38 (m, 2H), 7.85-7.99 (m, 3.7H), 8.14 - 8.18 (m, 0.3H).

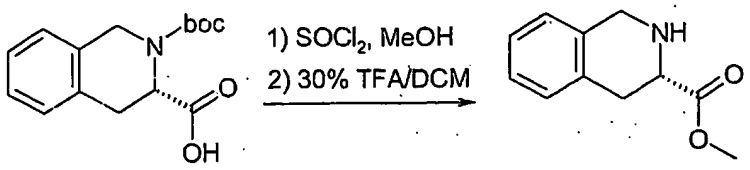
21		(V) rt 2.88, m/z 439 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.43 - 0.68 (m, 2H), 1.08 - 1.17 (m, 2H), 2.68 - 3.10 (m, 6H), 1H overlaps with the water signal, 4.34 – 4.71 (m, 3H), 6.22 - 6.34 (bs, 0.5H), 6.86 - 6.95 (bs, 0.5H), 7.07 - 7.23 (m, 6H), 7.28 - 7.39 (m, 2H), 7.75 - 7.94 (bs, 3H), 8.24 (s, 0.8H), 8.31 (s, 0.2H).
22		(V) rt 3.49, m/z 434 $(M+H)^+$.	
23		(V) rt 3.14, m/z 424 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ =2.79-3.31 (m, 6H), 3.75 (m, 1H), 4.51 – 4.74 (m, 2H), 4.97 - 5.07 (m, 1H), 7.05-7.39 (m, 6H), 7.77-7.97 (m, 3H).

24		(IV) rt 2.07, m/z 396 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.15-0.29 (m, 2H), 0.43-0.52 (m, 2H), 2.33-2.52 (m, 1H), 2.61 - 3.13 (m, 6H), 3.65-3.80 (m, 1H), 4.27 – 4.52 (m, 2H), 4.73 – 4.79 (m, 1H), 7.08-7.16 (m, 6H), 7.22 – 7.39 (m, 2H), 7.69-8.05 (m, 4H).
25		(V) rt 3.56, m/z 457 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.44 - 0.66 (m, 2H), 1.08 - 1.20 (m, 2H), 2.70 - 3.11 (m, 6H), 3.64 - 3.81 (m, 1H), 4.38 – 4.75 (m, 3H), 6.27 - 6.37 (bs, 0.5H), 6.92 - 6.98 (bs, 0.5H), 7.10 - 7.41 (m, 8H), 7.78 –7 .88 (bs, 3H), 8.28 (s, 0.2H), 8.32 (s, 0.2H).

Example 26



Steps 1 and 2



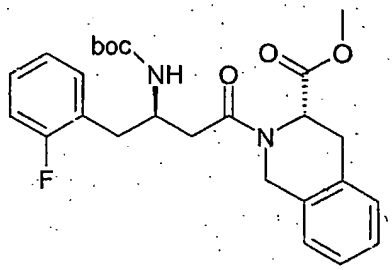
1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid methyl ester

3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester (50 mg, 0.18 mmol) is dissolved in 2 mL of methanol and 15 µL (0.20 mmol) thionylchloride are added. The solution is stirred at room temperature overnight. The solvent is evaporated under reduced pressure.

The crude material is dissolved in 2 mL of a 4 N HCl solution in dioxane. The solution is stirred at room temperature for 2 h, the solvent is evaporated under reduced pressure and the crude material is used in the next step without further purification.

LC/MS (IV) rt 1.72, m/z 192 $(M+H)^+$.

Step 3

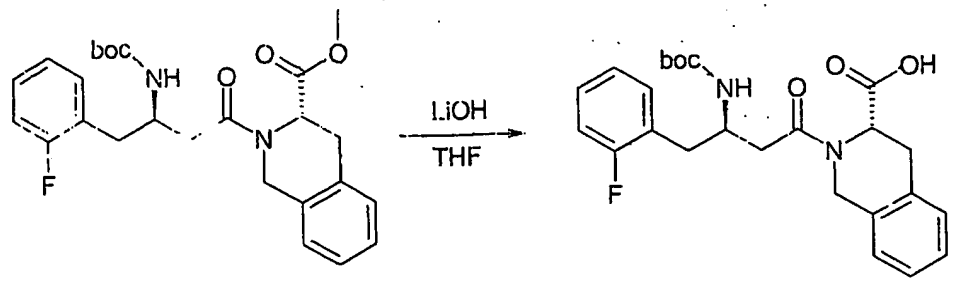


2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester

Obtained from 1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid methyl ester and Boc-(R)-3-amino-4-(2-fluoro-phenyl)-butyric acid according to the procedure described for step 3 in example 1.

LCMS (II) rt 3.30, m/z 471 $(M+H)^+$.

Step 4

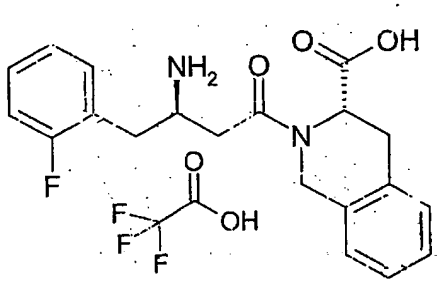


2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid

2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester (11 mg, 0.023 mmol) is dissolved in 1 mL THF and 46 µL of a 2N solution of lithium hydroxide in water is added at 0 °C. The reaction is stirred by room temperature overnight and another 40 µL of a 2N solution of lithium hydroxide in water are added. The solution is stirred by room temperature one day, the solvent is evaporated under reduced pressure and the crude product is used in the next step without further purification.

LC/MS (II) rt 2.92, 457 $(M+H)^+$.

Step 5



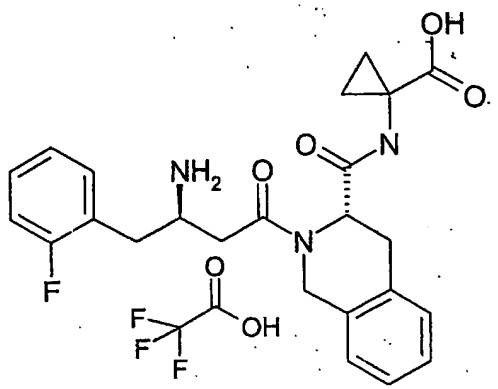
2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, trifluoroacetate salt

Obtained from the product from step 4 according to the procedure described for step 4 in example 1.

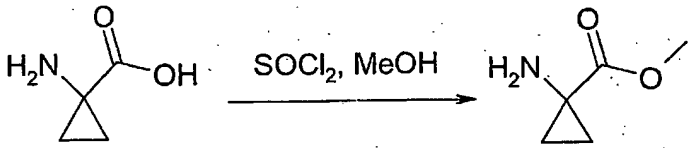
LCMS (IV) rt 1.98, m/z 357 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.68 - 3.25 (m, 6H), 3.71 - 3.78 (m, 1H), 4.34 - 4.69 (m, 2H), 4.87 – 4.90 and 5.10 - 5.14 (2m, 1H), 6.08 – 6.22 (m, 6H), 7.25 - 7.38 (m, 2H), 7.84 – 8.00 (m, 3H).

Example 27



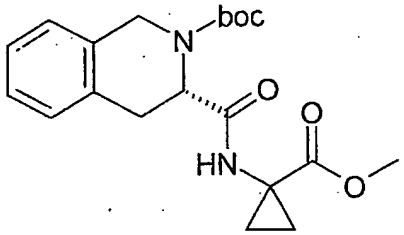
Step 1



1-Amino-cyclopropanecarboxylic acid methyl ester

1-Amino-cyclopropanecarboxylic acid (100 mg, 0.99 mmol) is dissolved in 100 mL of dry methanol and 73 µL (1.00 mmol) thionylchloride are added. The solution is stirred at room temperature overnight. The solvent is evaporated under reduced pressure and the crude material is used in the next step without further purification.

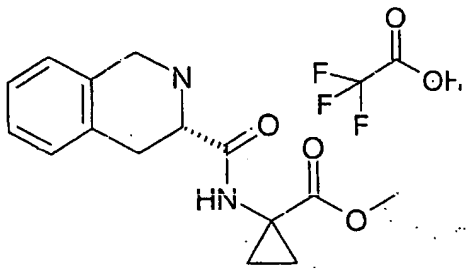
Step 2



3-(1-Methoxycarbonyl-cyclopropylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

Obtained from the product from step 1 according to the procedure described for step 1 in example 1.
LC/MS (II) rt 1.50, 397 $(M+H+Na)^+$.

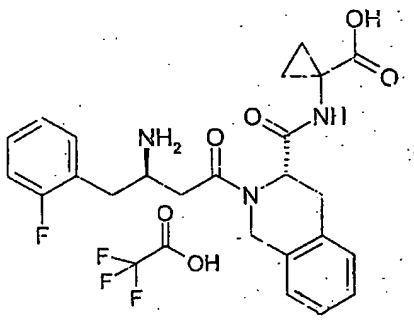
Step 3



1-[(1,2,3,4-Tetrahydro-isoquinoline-3-carbonyl)-amino]-cyclopropanecarboxylic acid methyl ester, trifluoroacetate salt

Obtained from the product from step 2 according to the procedure described for step 2 in example 1.
LC/MS (II) 1.86, 275 $(M+H)^+$.

Steps 4, 5 and 6

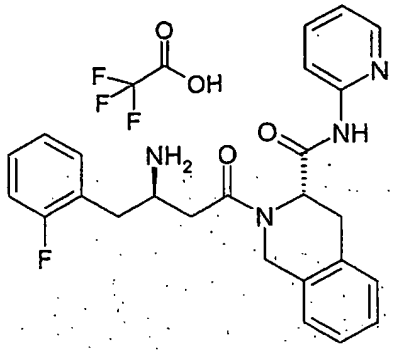


1-({2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carbonyl}-amino)-cyclopropanecarboxylic acid, trifluoroacetate salt

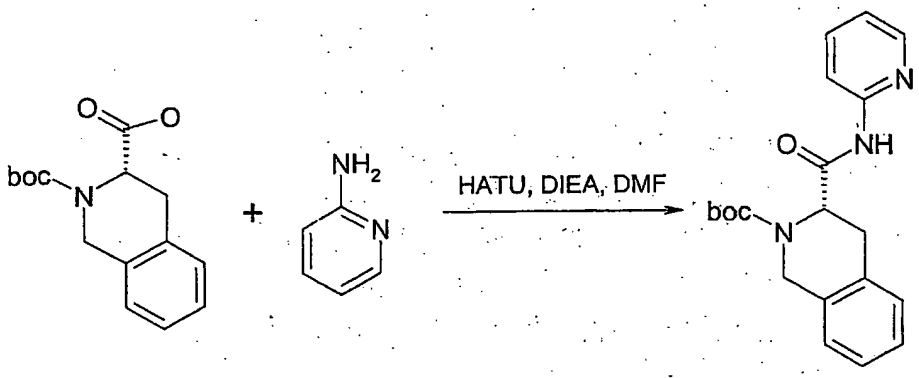
Obtained from the product from step 3 according to the procedure described for step 3-5 in example 26.
LC/MS (II) rt 2.08, 440 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.60-0.78 (m, 2H), 1.16-1.29 (m, 2H), 2.66-3.18 (m, 6H), 3.71-3.80 (m, 1H), 4.32 – 4.76 (m, 2H), 4.93-4.96 (m, 1H), 7.07-7.21 (m, 6H), 7.24-7.34 (m, 2H), 7.87 (bs, 3H), 8.26 (s, 0.7H), 8.49 (s, 0.3H).

Example 28



Step 1

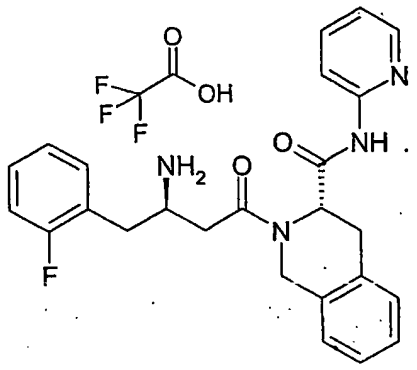


3-(Pyridin-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

A mixture of 20 mg (0.07 mmol) 3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester (Boc-TIC-OH), 30 mg (0.08 mmol) N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), 10 mg (0.11 mmol) 2-aminopyridine and 25 µL (0.14 mmol) diisopropylethylamine (DIEA) in 2 mL N,N-dimethylformamide is stirred at room temperature overnight. The solution is diluted with 50 mL ethyl acetate, washed with saturated aqueous sodium carbonate solution and dried over sodium sulphate. The solvent is removed by reduced pressure. Purification by flash chromatography (silica gel, cyclohexane to ethyl acetate) affords the title compound.

LCMS (II) rt 2.40, m/z 354 (M+H)+.

Step 2-4

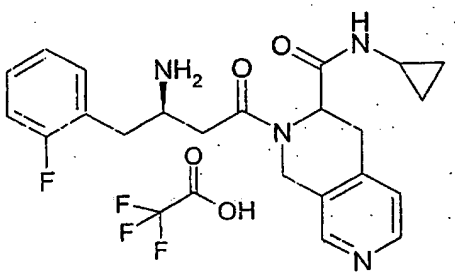


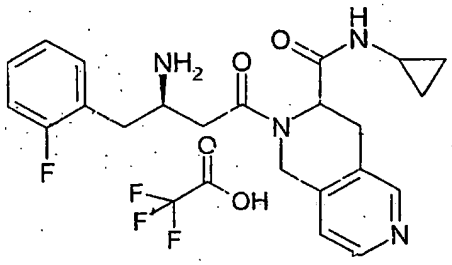
2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid pyridin-2-ylamide, trifluoroacetate salt

Obtained from the product from step 1 according to the procedures described for steps 2-4 in example 1.

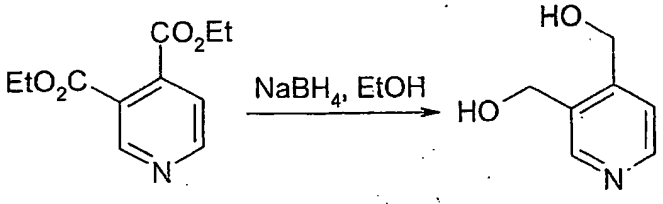
LCMS (II) rt 2.05, m/z 433 $(M+H)^+$.

Example 29





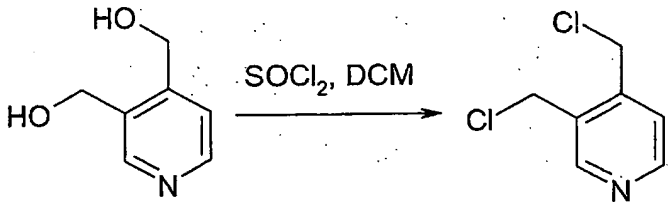
Step 1



3,4-Bis(hydroxymethyl)pyridine

Sodium borohydride (8.5 g, 225 mmol) is dissolved in ethanol (130 mL) and diethyl 3,4-pyridinedicarboxylate (10 g, 45 mmol) is added in portions to the solution under ice-cooling. The resulting mixture is refluxed overnight. After ethanol (130 mL) has been added to the hot reaction mixture, insoluble matter is removed by filtration while the diluted mixture is still hot. The filtrate is concentrated under reduced pressure. The obtained residue is purified by column chromatography (silica gel, dichloromethane/methanol/NH_4OH =100:10:1) to give the title compound.
LCMS (II) rt 0.29, m/z 140 $(M+H)^+$.

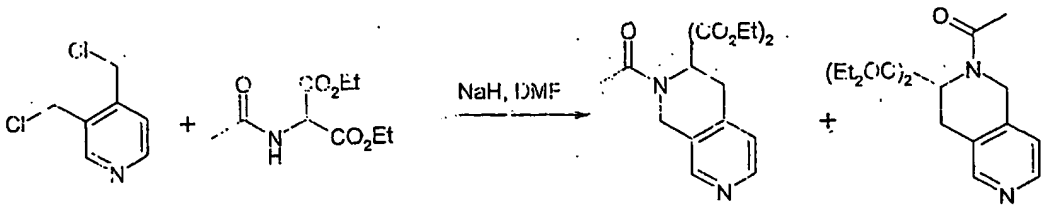
Step 2



3,4-Bis(chloromethyl)pyridine

Thionyl chloride (30 mL) is added to a solution of 3,4-bis(hydroxymethyl)pyridine (5.68 g, 41 mmol) in dichloromethane (15 mL) at 0 °C, and then the resulting mixture is refluxed for 1 hour. After having been cooled to room temperature, the reaction mixture is concentrated under reduced pressure and the crude product is dissolved in a saturated aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The organic layer is washed with brine, dried over magnesium sulphate, and concentrated under reduced pressure. The obtained residue is purifed by column chromatography (silica gel, 0% to 10% ethyl acetate in cyclohexane) to give the title compound.
LCMS (II) rt 1.63, m/z 176 $(M+H)^+$.

Step 3



2-(2-Acetyl-1,2,3,4-tetrahydro-[2,7]naphthyridin-3-yl)-malonic acid diethyl ester and 2-(2-acetyl-1,2,3,4-tetrahydro-[2,6]naphthyridin-3-yl)-malonic acid diethyl ester

Diethyl acetamidomalonate (934 mg, 4.3 mmol) and sodium hydride (60%, 343 mg, 5.60 mmol) are successively added at room temperature to a solution of 3,4-bis(chloromethyl)pyridine (757 mg, 4.30 mmol) (step 2) in dichloromethane (4 mL), and the resulting mixture is stirred at room temperature for 30 min. Further sodium hydride (60%, 171 mg, 4.30 mmol) is added to the reaction mixture, and then the resulting mixture is stirred at room temperature overnight. The reaction mixture is diluted with water (500 mL) and extracted with ethyl acetate. The organic layer is washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The oil obtained is purified with column chromatography (silica gel, 0% to 10% methanol in ethyl acetate) to give a 1:8 mixture of the regioisomer title compounds.

LCMS (II) rt 1.64, m/z 321 $(M+H)^+$.

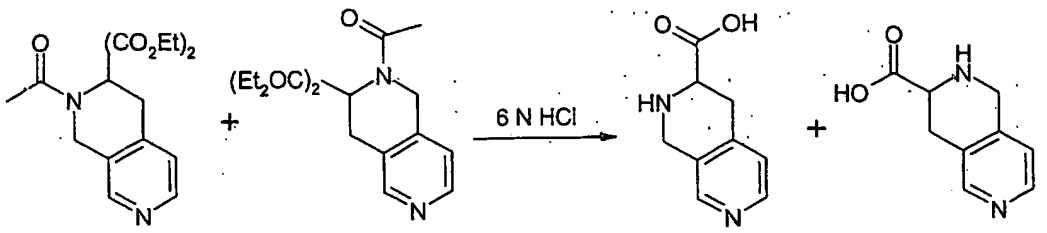
Major isomer:

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 1.08 (t, 6H), 2.19 (s, 3H), 3.34 (s, 2H), 4.07 (q, 4H), 4.11 (s, 2H), 7.26 - 7.28 (m, 1H), 8.38 - 8.40 (m, 2H).

Minor isomer:

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 1.18 (m, 6H), 1.92 (s, 3H), 4.09 - 4.16 (m, 4H), 8.45 (m, 2H). The other signals overlap with the signals of the major isomer.

Step 4

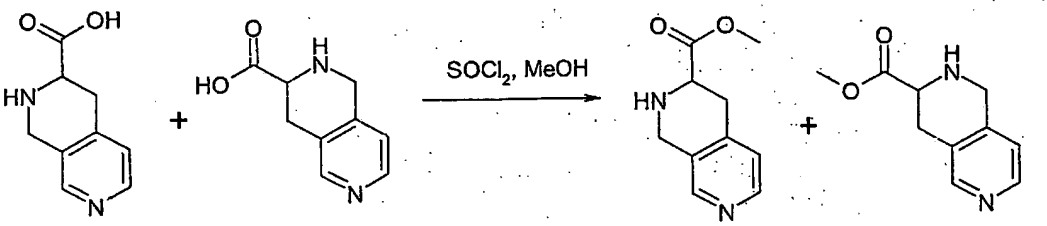


1,2,3,4-Tetrahydro-[2,7]naphthyridine-3-carboxylic acid and 1,2,3,4-Tetrahydro-[2,6]naphthyridine-3-carboxylic acid

Hydrochloric acid (6 N, 4 mL) is added to a mixture of 2-(2-acetyl-1,2,3,4-tetrahydro-[2,7]naphthyridin-3-yl)-malonic acid diethyl ester and 2-(2-acetyl-1,2,3,4-tetrahydro-[2,6]naphthyridin-3-yl)-malonic acid diethyl ester (440 mg, 1.37 mmol) (step 3) and the resulting mixture is refluxed for 3 hours. After being cooled to room temperature, the reaction mixture is concentrated under reduced pressure. The crude product is used in the next step without further purification.

LCMS (II) rt 0.25, m/z 179 $(M+H)^+$.

Step 5

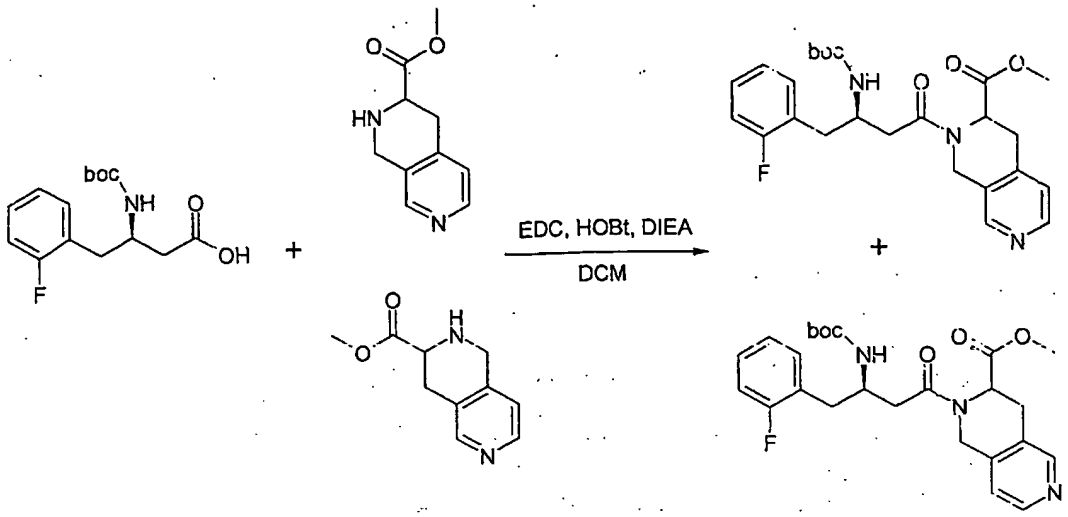


1,2,3,4-Tetrahydro-[2,7]naphthyridine-3-carboxylic acid methyl ester and 1,2,3,4-Tetrahydro-[2,6]naphthyridine-3-carboxylic acid methyl ester

Thionyl chloride (625 mg, 1.75 mmol) in 3.2 mL of dry methanol is added at room temperature to a mixture of 1,2,3,4-tetrahydro-[2,7]naphthyridine-3-carboxylic acid and 1,2,3,4-tetrahydro-[2,6]naphthyridine-3-carboxylic acid (320 mg, 1.75 mmol) and then the resulting mixture is refluxed overnight. After having been cooled to room temperature, the reaction mixture is concentrated under reduced pressure. Dioxane (25 mL) is added to the obtained residue, and then the resulting mixture is concentrated under reduced pressure to give a mixture of the title compounds.

LCMS (II) rt 0.26, m/z 193 $(M+H)^+$.

Step 6

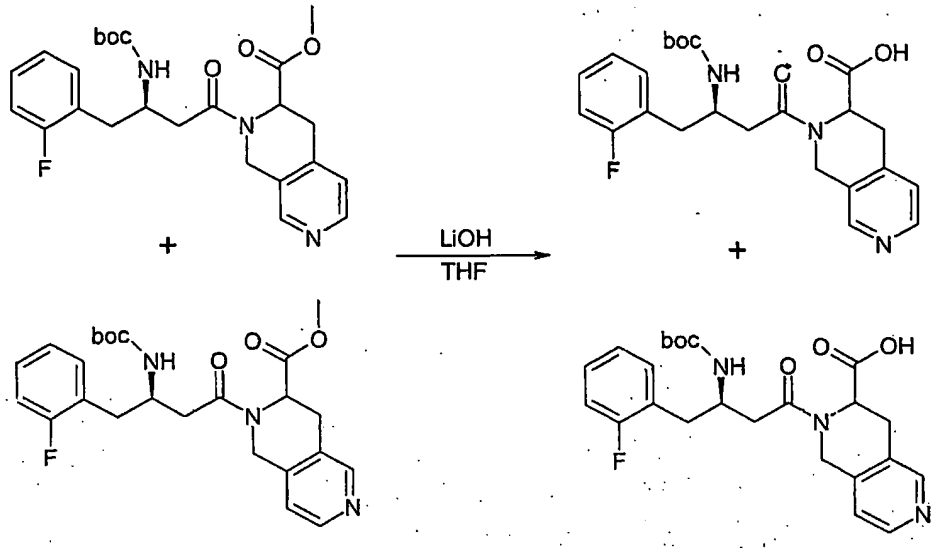


2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,7]naphthyridine-3-carboxylic acid methyl ester and 2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,6]naphthyridine-3-carboxylic acid methyl ester

To a solution of 112 mg (0.38 mmol) Boc-(R)-3-amino-4-(2-fluoro-phenyl)-butyric acid in 1 mL dichloromethane 79 mg (0.41 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 56 mg (0.41 mmol) 1-hydroxybenzotriazole (HOBt) and 197 µL (1.13 mmol) diisopropylethylamine (DIEA) are added and after 30 minutes the crude material from step 5 (0.14 mmol). The mixture is stirred overnight at room temperature and concentrated under reduced pressure. The crude product is used in the next step without further purification.

LCMS (II) rt 2.56, m/z 472 $(M+H)^+$

Step 7

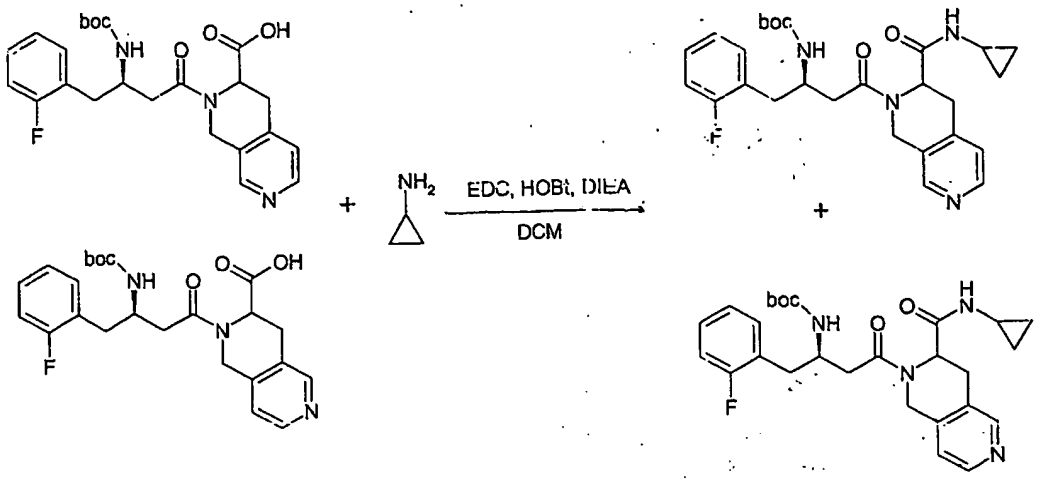


2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,7]naphthyridine-3-carboxylic acid and 2-[3-tert-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,6]naphthyridine-3-carboxylic acid

The crude material from step 6 (504 mg, 1.07 mmol) is dissolved in 2.1 mL THF and 2.1 mL of a 2N solution of lithium hydroxide in water is added. The reaction is stirred at room temperature overnight, the solvent is evaporated under reduced pressure and the crude product is used in the next step without further purification.

LC/MS (II) rt 2.07, 458 $(M+H)^+$.

Step 8

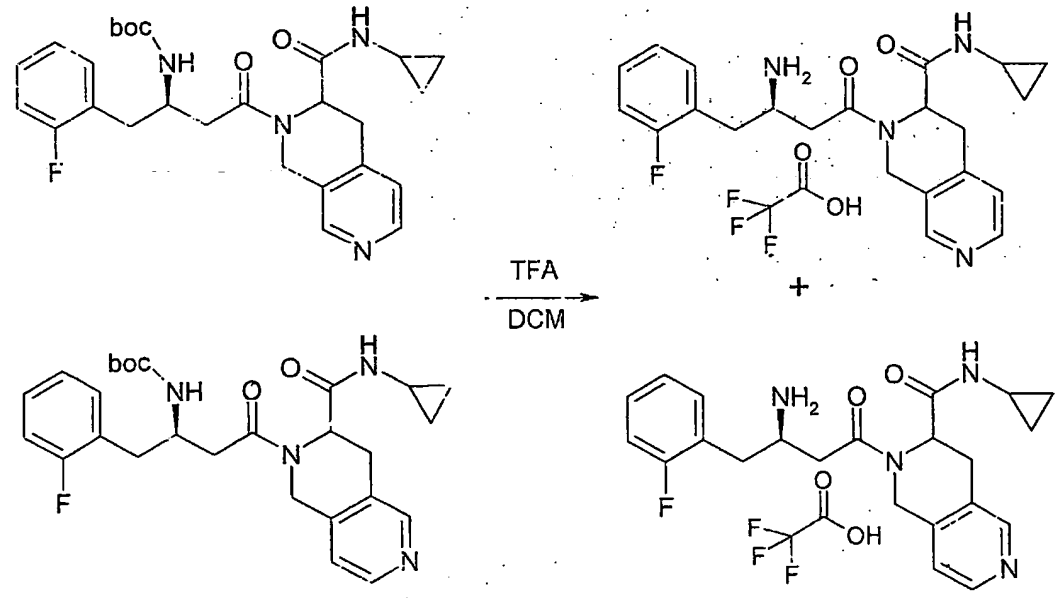


[3-(3-Cyclopropylcarbamoyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-1-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid tert-butyl ester and [3-(3-Cyclopropylcarbamoyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-1-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid tert-butyl ester

Obtained from the product from step 7 according to the procedures described for step 6 in this example using cyclopropylamine

LCMS (II) rt 2.17, m/z 497 $(M+H)^+$.

Step 9

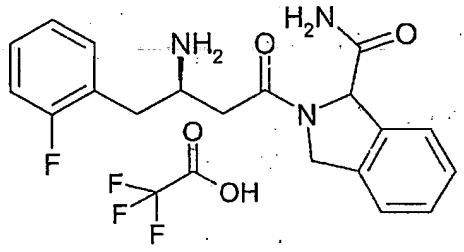


2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,7]naphthyridine-3-carboxylic acid cyclopropylamide. trifluoroacetate salt and 2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-1,2,3,4-tetrahydro-[2,6]naphthyridine-3-carboxylic acid cyclopropylamide. trifluoroacetate salt

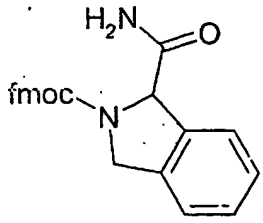
Obtained from the product from step 8 according to the procedures described for step 4 in example 1. The crude pruduct is purified by HPLC chromatography to give a mixture of the four isomers (2 regioisomer each as mixture of 2 diastereomers) as TFA-salts.
LCMS (VI) rt 5.14 (only 1 peak for 4 isomers), m/z 397 $(M+H)^+$.
^{1}H-NMR for mixture of 4 isomers (300 MHz, DMSO-d_6) δ = 0.19-0.38 (m, 2H), 0.42-0.62 (m, 2H), 2.32-2.50 (m, 1H), 2.60-3.50 (m, 6H), 3.48-3.67 (m, 1H), 4.35-5.18 (m, 3H), 7.02-7.18 (m, 2H), 7.27-7.39 (m, 2H), 7.61-7.71 (m, 1H), 7.85-8.21 (m, 3H), 8.53-8.73.

The 4 isomers (2 regioisomers with two diastereomers each) are separated via chiral HPLC. The retention times are as follows:
Isomer 1: 12.77 min; Isomer 2: 14.69 min; Isomer 3: 21.87 min; Isomer 4: 32.66 min.
The absolute configuration for the 4 isomers is not assigned.

Example 30



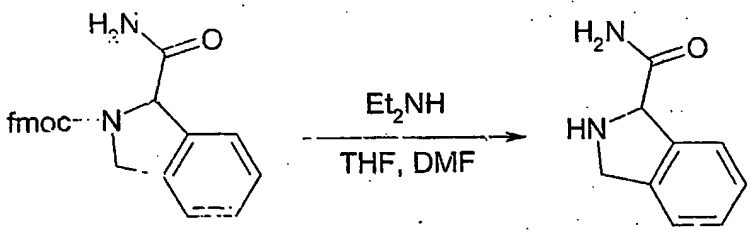
Step 1



1-Carbamoyl-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester

Obtained from 1,3-dihydro-isoindole-1,2-dicarboxylic acid 2-tert-butyl ester according to the procedure described for step 1 in example 1.
LC/MS (IV) rt 2.90, 384 $(M+H)^+$.

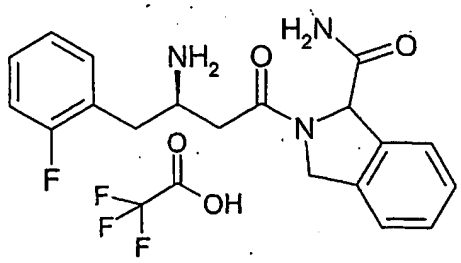
Step 2



2,3-Dihydro-1H-isoindole-1-carboxylic acid amide

1-Carbamoyl-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester (step 1) is suspended in 2 mL of a 20% solution of diethylamine in tetrahydrofuran. To the suspension drops of *N,N*-dimethylformamide are added until complete dissolution of the solid. The solution is stirred until the starting material disappears on thin layer chromatography. The solvent is removed under reduced pressure. The crude product is dissolved in ethyl acetate and extracted with a 5% HCl solution. The aqueous phase is basified to pH 8-9 and extracted with dichloromethane. The resulting organic layer is dried over sodium sulphate and concentrated under reduced pressure The crude material is taken directly to the next step.
LCMS (II) rt 1.46, m/z 163 $(M+H)^+$

Step 3 and 4

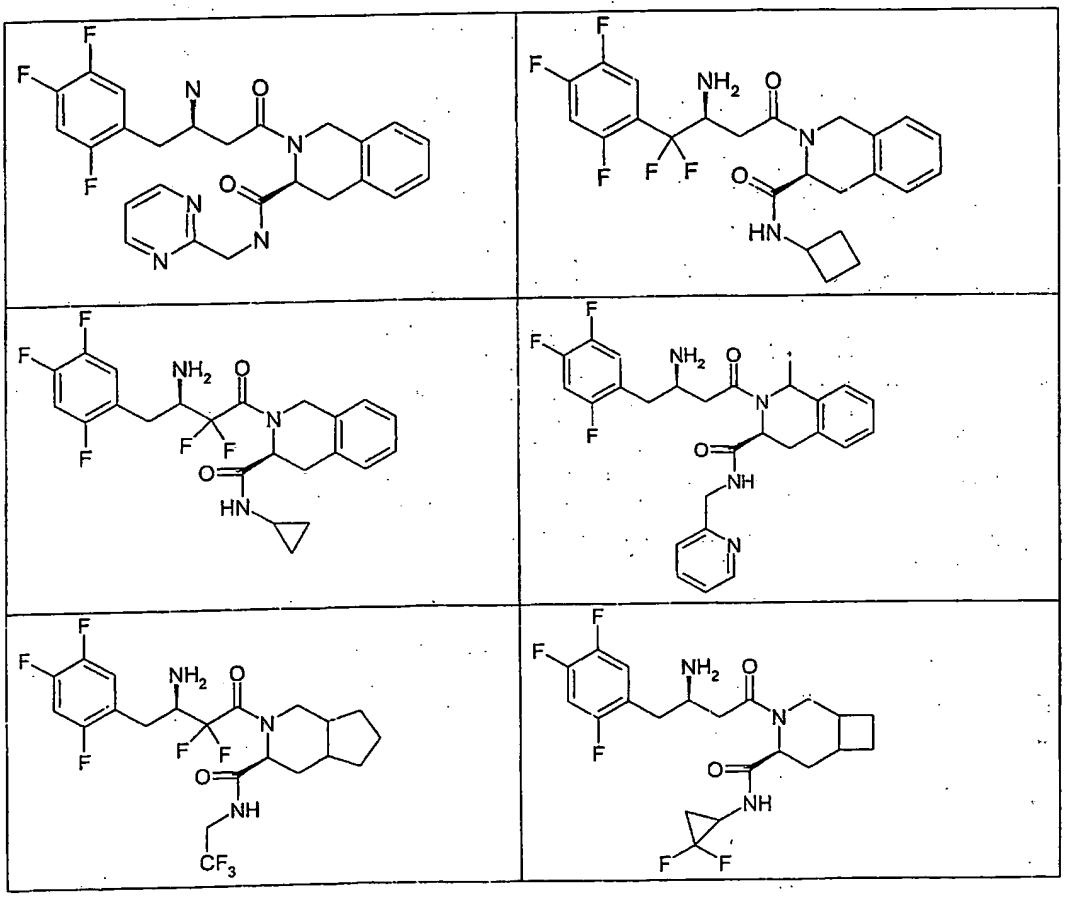


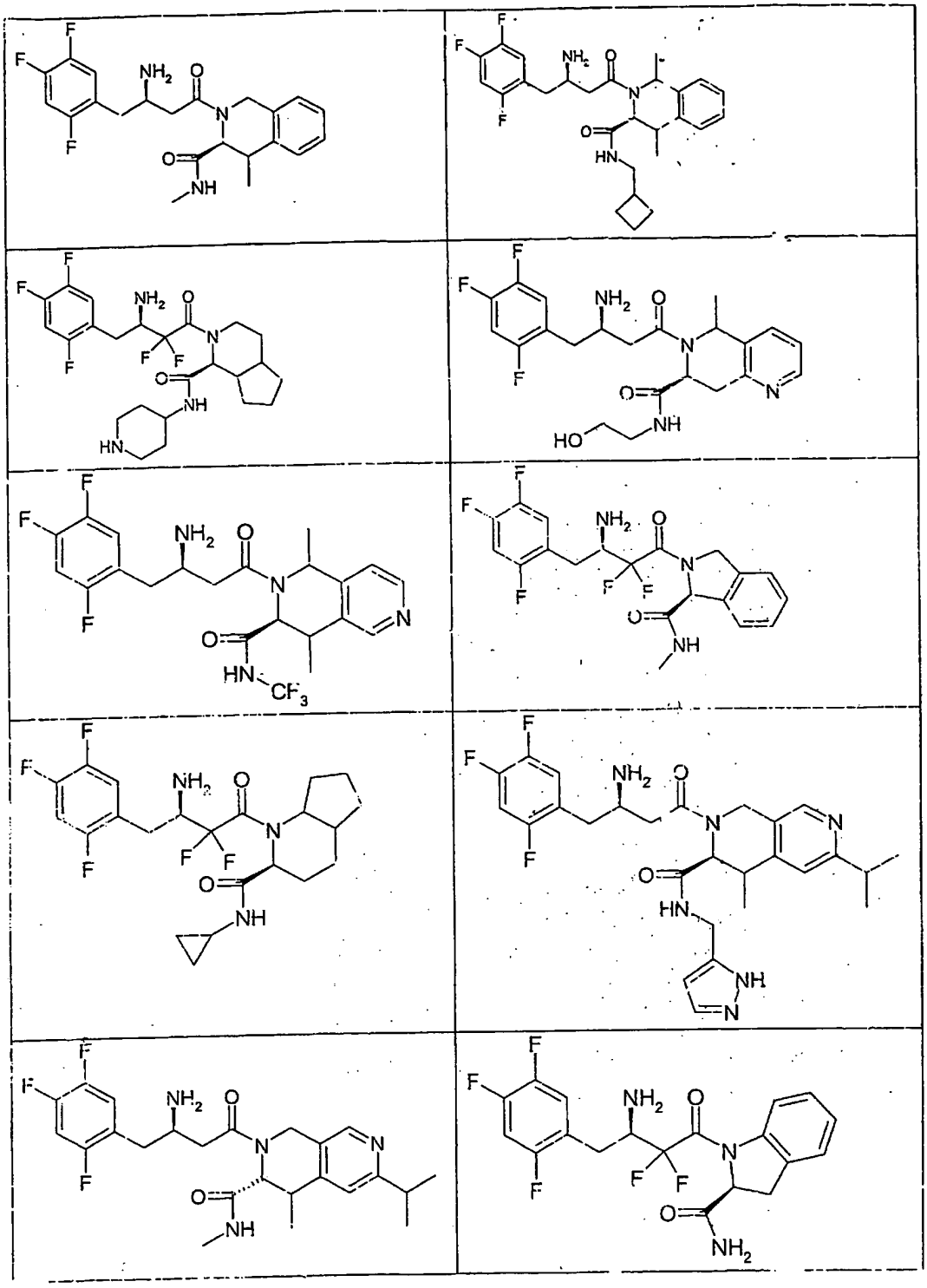
2-[3-Amino-4-(2-fluoro-phenyl)-butyryl]-2,3-dihydro-1H-isoindole-1-carboxylic acid amide, trifluoroacetate salt

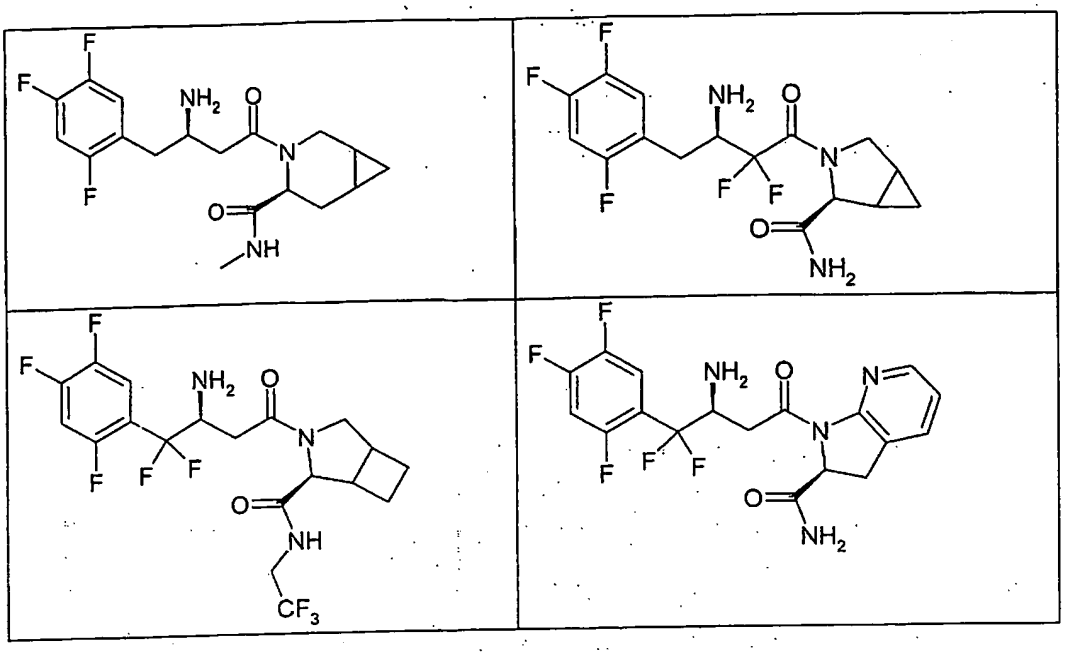
Obtained from the product from step 2 according to the procedure described for step 3 and step 4 in example 1.

LC/MS (II) rt 2:06, 342 $(M+H)^+$.

Further examples from this series are exemplified below:







ASSAYS

Inhibition of DPP-IV peptidase activity was monitored with a continuous fluorimetric assay. This assay is based on the cleavage of the substrate Gly-Pro-AMC (Bachem) by DPP-IV, releasing free AMC. The assay is carried out in 96-well microtiterplates. In a total volume of 100 µL, compounds are preincubated with 50 pM DPP-IV employing a buffer containing 10mM Hepes, 150mM NaCl, 0.005% Tween 20 (pH 7.4). The reaction is started by the addition of 16 µM substrate and the fluorescence of liberated AMC is detected for 10 minutes at 25 °C with a fluorescence reader (BMG-Fluostar; BMG-Technologies) using an excitation wavelength of 370 nm and an emission wavelength of 450 nm. The final concentration of DMSO is 1 %. The inhibitory potential of the compounds were determined. DPP-IV activity assays were carried out with human and porcine DPP-IV (see below); both enzymes showed comparable activities-include.

Soluble human DPP-IV lacking the transmembrane anchor (Gly31-Pro766) was expressed in a recombinant YEAST-strain as Pre-Pro-alpha-mating fusion. The secreted product (rhuDPP-IV-Gly31-Pro766) was purified from fermentation broth (>90% purity) and used for inhouse screening.

In the table are listed the IC_{50} values for inhibition of DPP-IV peptidase activity determined in assays as described above. The IC_{50} values were grouped in 3 classes: a ≤ 100 nM; b ≥101 nM and ≤ 1001 nM ; C ≥1001 nM ≤ 2000 nM.

Example	IC_{50}
1	a
2	a
3	b
4	b
5	c
6	a
7	a
8	a
9	a

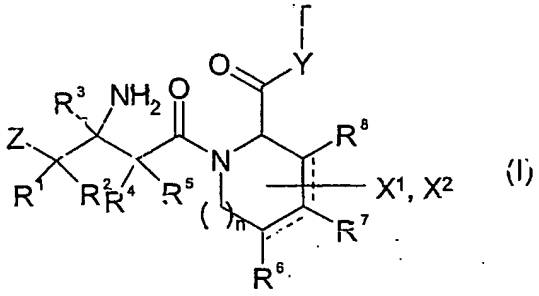
Example	IC_{50}
10	a
11	a
12	a
13	a
14	a
15	a
16	a
17	a
18	a

Example	IC_{50}
19	a
20	a
21	a
22	a
23	a
24	b
25	a
26	b
27	a

Example	IC_{50}
28	a
29 (isomer 1)	a
29 (isomer 2)	a
29 (isomer 3)	a
29 (isomer 4)	a
30	b

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein a dotted line indicates an optionally present double bond and wherein

Z is selected from the group consisting of
phenyl;
naphthyl;
C_{3-7} cycloalkyl;
heterocycle; and
heterobicycle;
wherein Z is optionally substituted with one, or independently from each other, more of
halogen;
CN;
OH;
=O, where the ring is at least partially saturated;
C_{1-6} alkyl, optionally substituted with one or more F; and
O-C_{1-6} alkyl, optionally substituted with one or more F;

R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of
H;
F;
OH;
C_{1-6} alkyl, optionally substituted with one or more F; and
O-C_{1-6} alkyl, optionally substituted with one or more F;

and/or R^1 and R^2 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^2 and R^3 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^3 and R^4 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^4 and R^5 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

R^3 is H or C_{1-6} alkyl;

n is 0, 1 or 2;

X^1 is selected from the group consisting of
H;
F;
OH; and
C_{1-6} alkyl, optionally substituted with one or more F;

X^2 is selected from the group consisting of
H;
F; and
C_{1-6} alkyl, optionally substituted with one or more F;

R^6 and R^7 form together a ring A, provided that R^8 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more F;
or
R^8 and R^7 form together a ring A, provided that R^6 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more F;

A is selected from the group consisting of
phenyl;
wherein phenyl is optionally substituted with one, or independently from each other, more of

halogen;
CN;
COOH;
OH;
$C(O)NH_2$;
$S(O)_2NH_2$;
C_{1-6} alkyl;
O-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^9)$- C_{1-6} alkyl;
$S(O)_2N(R^{10})$-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; or
$N(R^{11})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one or more F;

heterocycle; and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl and heterocycle are optionally substituted with one, or independently from each other, more of

halogen;
CN;
OH;
=O, where the ring is at least partially saturated;
NH_2
COOH;
$C(O)NH_2$;
$S(O)_2NH_2$;
C_{1-6} alkyl;
O-C_{1-6} alkyl;
$N(R^9)$-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{10})$- C_{1-6} alkyl;
$N(R^{11})$-C(O)-C_{1-6} alkyl;
$S(O)_2N(R^{12})$-C_{1-6} alkyl;

$S(O)_2$-C_{1-6} alkyl; or

$N(R^{13})S(O)_2$-C_{1-6} alkyl;

and wherein R^9, R^{10}, R^{11}; R^{12}, R^{13} are independently from each other H or C_{1-6} alkyl optionally substituted with one or more F;

Y is -O- or -$N(R^{14})$-;

R^{14}, T are independently from each other T^1-T^2 or T^2;

T^1 is selected from the group consisting of

-C_{1-6} alkyl-;

-$S(O)_2$-C_{1-6} alkyl-;

-C_{1-6} alkyl-O-; and

-C_{1-6} alkyl-$N(R^{15})$-;

wherein each C_{1-6} alkyl is optionally substituted with one or more F or OMe;

R^{15} is H or C_{1-6} alkyl, optionally substituted with one or more F;

T^2 is selected from the group consisting of

H;

CF_3;

phenyl;

wherein phenyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

R^{16};

COOH;

OH;

$C(O)NH_2$; or

$S(O)_2NH_2$;

C_{3-7} cycloalkyl; and

heterocycle;

wherein C_{3-7} cycloalkyl and heterocycle are optionally substituted with one, or independently from each other, more of

halogen;
CN;
R^{17};
OH;
=O, where the ring is at least partially saturated;
NH_2
COOH;
$C(O)NH_2$; or
$S(O)_2NH_2$;

When R^{14} is T^1-T^2 and represents C_{1-6} alkyl and T is T^1-T^2 and represents -C_{1-6} alkyl, C_{1-6} alkyl-O- or -C_{1-6} alkyl-N(R^{15})-, then R^{14} and T may form together a 3 to 7 membered cyclic group, which contains 1 N and optionally 1 further O or N, whereby this cyclic group may be further substituted;

R^{16} is selected from the group consisting of
C_{1-6} alkyl;
)-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
)C(C)- C_{1-6} alkyl;
(O)N(R^{18})- C_{1-6} alkyl;
(O)$_2$N(R^{19})-C_{1-6} alkyl;
(O)-C_{1-6} alkyl;
S(O)$_2$-C_{1-6} alkyl; and
N(R^{20})S(O)$_2$-C_{1-6} alkyl;
wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{21}$, $C(O)N(R^{22}R^{23})$, $S(O)_2N(R^{24}R^{25})$, OR^{26}, or $N(R^{27}R^{28})$;

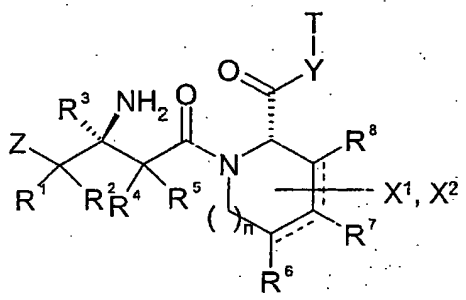
R^{17} is selected from the group consisting of
C_{1-6} alkyl;
-C_{1-6} alkyl;
N(R^{18})-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;

$C(O)N(R^{19})$- C_{1-6} alkyl;
$N(R^{20})$-$C(O)$-C_{1-6} alkyl;
$S(O)_2N(R^{21})$-C_{1-6} alkyl;
$S(O)$-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; and
$N(R^{22})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{23}$, $C(O)N(R^{24}R^{25})$, $S(O)_2N(R^{26}R^{27})$, OR^{28}, or $N(R^{29}R^{30})$;

R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30} are independently from each other H or C_{1-6} alkyl.

2. A compound according to claim 1 of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1-R^8, n, X, Y and T have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is phenyl or heterocycle and Z is optionally substituted independently from each other with up to 2 of Cl, F, CN, or C_{1-6} alkyl.

4. A compound according to any one of the preceding claims, wherein R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of H, F, OH and C_{1-6} alkyl.

5. A compound according to any one of the preceding claims, wherein R^3 is H.

A compound according to any one of the preceding claims, wherein n is 0 or 1.

A compound according to any one of the preceding claims, wherein X^1 and X^2 are independently from each other H or F.

8. A compound according to any one of the preceding claims, wherein R^6 and R^7 form together a ring A and R^8 is H or F.

9. A compound according to any one of the preceding claims, wherein A is selected from the group consisting of

phenyl;

wherein phenyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

COOH;

OH;

$C(O)NH_2$;

$S(O)_2NH_2$;

C_{1-6} alkyl;

O-C_{1-6} alkyl;

COO-C_{1-6} alkyl;

$OC(O)$- C_{1-6} alkyl;

$C(O)NH$- C_{1-6} alkyl;

$S(O)_2NH$-C_{1-6} alkyl;

$S(O)_2$-C_{1-6} alkyl; or

$NHS(O)_2$-C_{1-6} alkyl;

and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;
NH_2
COOH;
$C(O)NH_2$;
$S(O)_2NH_2$;
C_{1-6} alkyl;
O-C_{1-6} alkyl;
NH-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
C(O)NH- C_{1-6} alkyl;
NH-C(O)-C_{1-6} alkyl;
$S(O)_2$NH-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; or
$NHS(O)_2$-C_{1-6} alkyl;

10. A compound according to any one of the preceding claims, wherein Y is -N(R^{31})- and R^{31} is H.

11. A compound according to any one of the preceding claims, wherein T is T^2 and T^2 is H.

12. A compound according to any one of the preceding claims, wherein T^1 is C_{1-6} alkyl.

13. A compound according to any one of the preceding claims, wherein T^2 is selected from the group consisting of
phenyl;
wherein phenyl is optionally substituted with one, or independently from each other, more of
halogen;
CN;
COOH;
OH;
$C(O)NH_2$; or
$S(O)_2NH_2$;

and

C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;

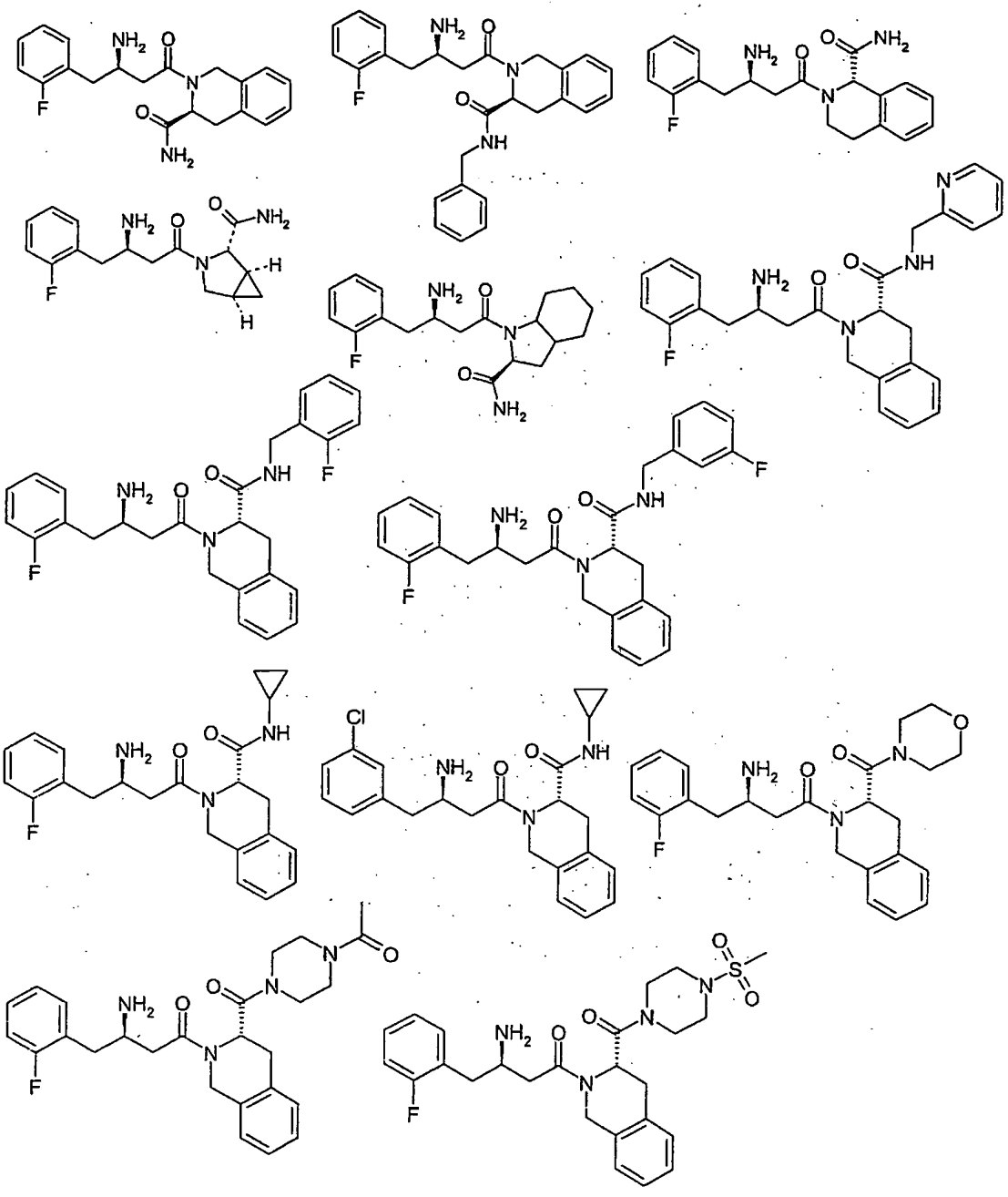
NH_2

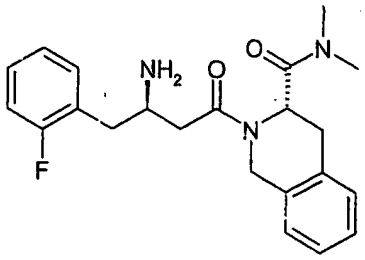
COOH;

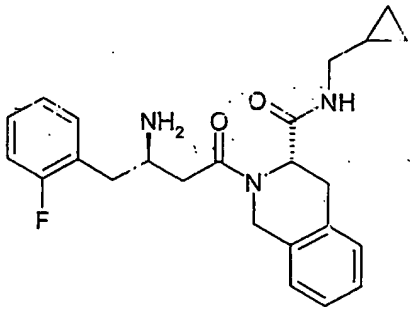
$C(O)NH_2$; or

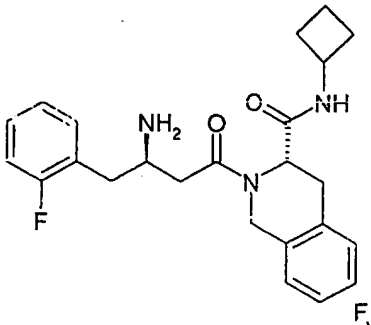
$C(O)_2NH_2$.

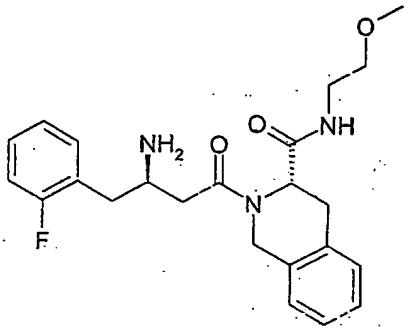
14. A compound according to claim 1 selected from the group consisting of

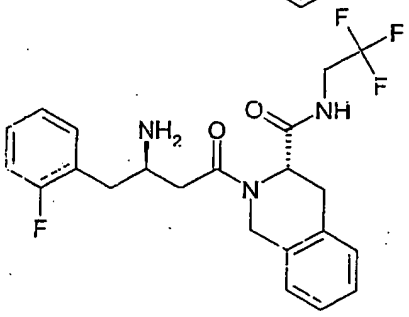


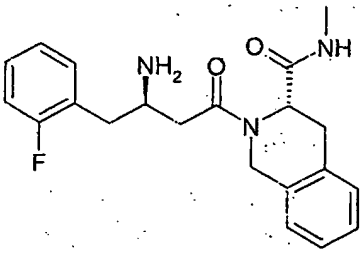


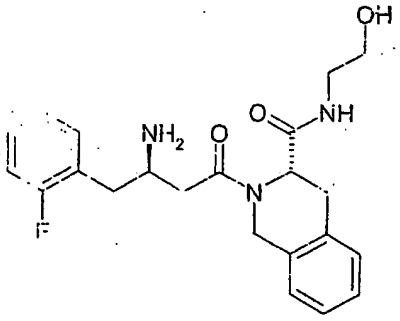


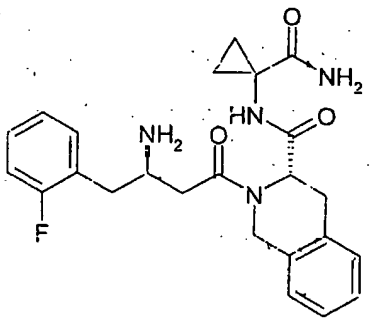


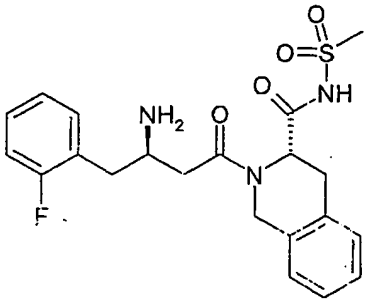


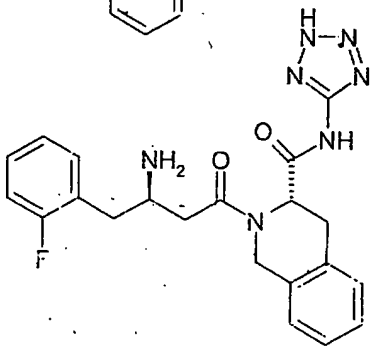


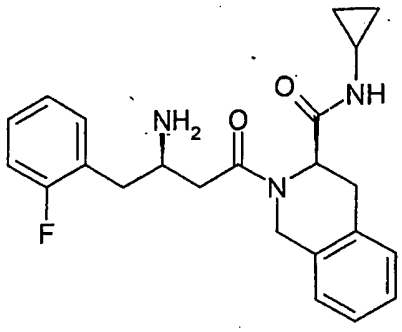
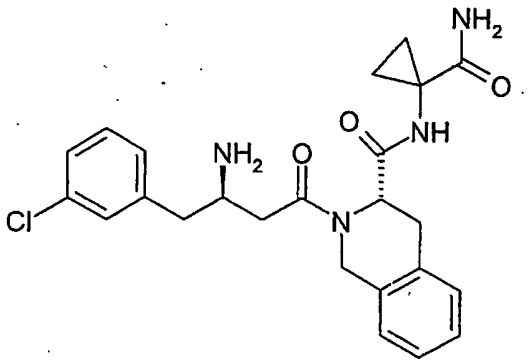
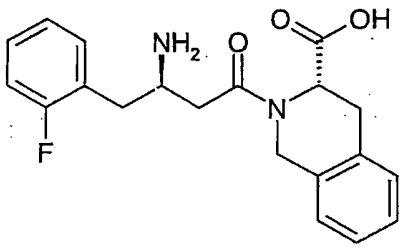
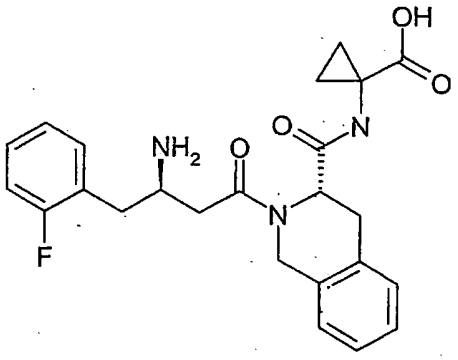
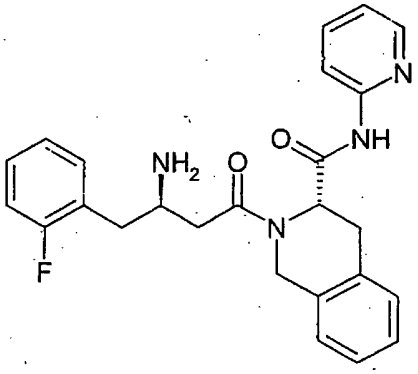
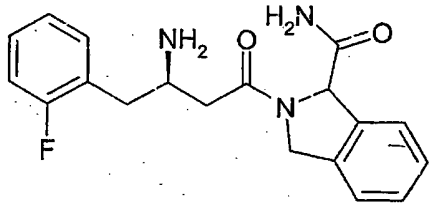
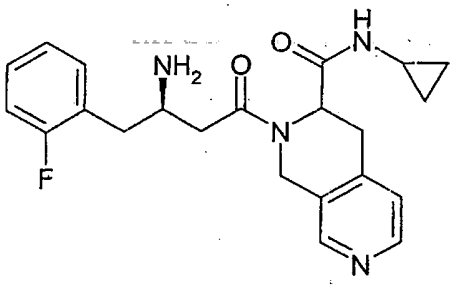
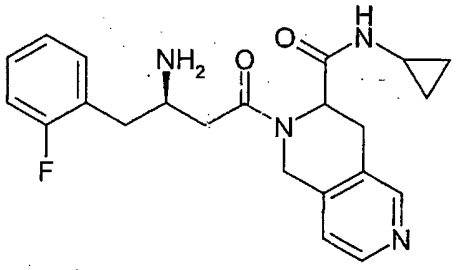










or a pharmaceutically acceptable selt of the above.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/014039

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 C07D209/42 C07D209/52 C07D217/26 C07D401/12
C07D471/04 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/007468 A (MERCK & CO., INC., USA) 22 January 2004 (2004-01-22) claim 1	1-22
Y	WO 03/000180 A (MERCK & CO., INC., USA) 3 January 2003 (2003-01-03) claims 1,21	1-22
Y	WO 03/000181 A (MERCK & CO., INC., USA) 3 January 2003 (2003-01-03) claims 1,13	1-22
Y	WO 03/082817 A (KIM DOOSEOP ;PARMEE EMMA R (US); WEBER ANN E (US); DUFFY JOSEPH L) 9 October 2003 (2003-10-09) claims 1,24	1-22

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2005	25/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bérillon, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/014039

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/083128 A (SQUIBB BRISTOL MYERS CO ;ROBL JEFFREY A (US); SULSKY RICHARD B (US) 24 October 2002 (2002-10-24) claims 1,12	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/014039

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 20 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/014039

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			WO	03000180 A2	03-01-2003
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			EP	1377288 A1	07-01-2004
			HU	0401423 A2	29-11-2004
			JP	2004532220 T	21-10-2004
			WO	02083128 A1	24-10-2002
			US	2002183367 A1	05-12-2002